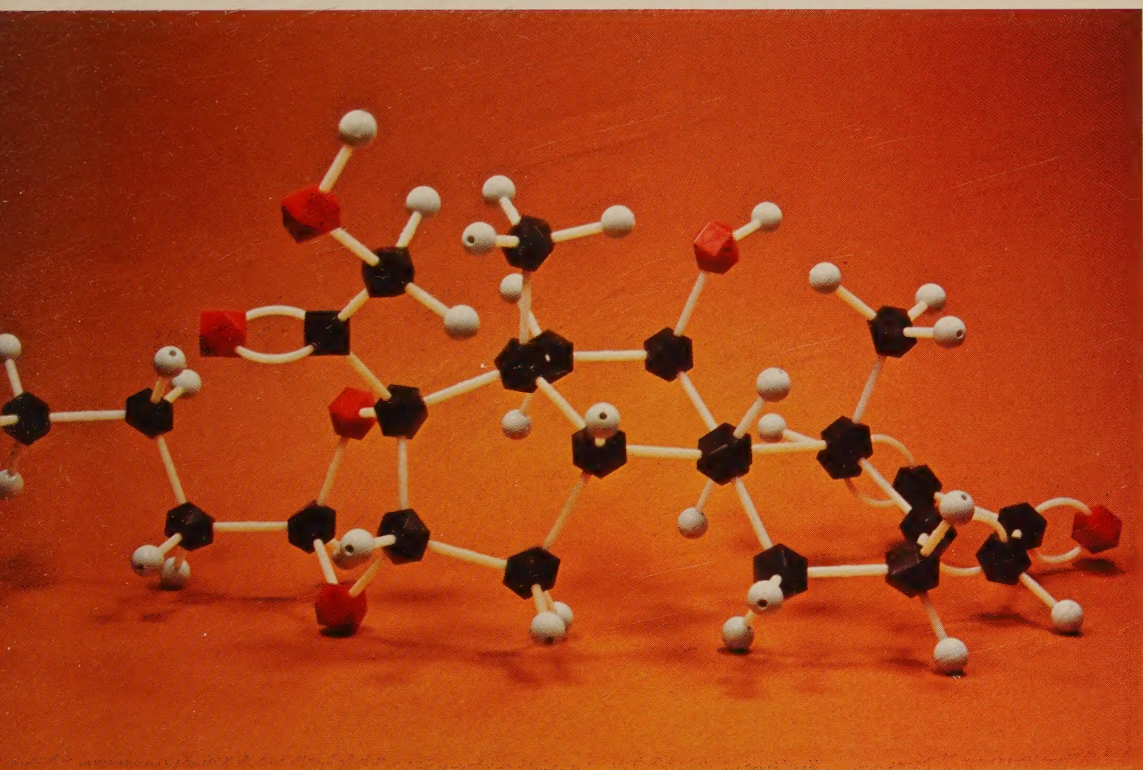


Evaluation of Budesonide

- a new glucocorticosteroid
for local treatment of
bronchial asthma

by S-Å JOHANSSON



LUND 1983

Evaluation of Budesonide

- a new glucocorticosteroid

for local treatment of bronchial asthma

by

STEN-ÅKE JOHANSSON

AKADEMISK AVHANDLING

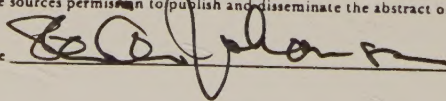
som för avläggande av doktorsexamen i medicinsk vetenskap vid Lunds
Universitet offentligen försvaras i föreläsningssal F1, Lunds
Lasarett, måndagen den 12 december 1983 klockan 09.15.

LUND 1983

Organization LUND UNIVERSITY		Document name DOCTORAL DISSERTATION	
Department of Clinical Pharmacology University Hospital S-221 85 LUND, SWEDEN		Date of issue 1983-11-21	
Author(s) Sten-Ake Johansson		CODEN: LUMEDW/(MECF-1003)/1-50(1983)	
		Sponsoring organization	
Title and subtitle EVALUATION OF BUDESONIDE A new corticosteroid for local treatment of bronchial asthma			
Abstract Budesonide is a synthetic glucocorticosteroid with a high first-pass metabolism and an improved ratio between topical anti-inflammatory and systemic effects. The ability of inhaled budesonide to inhibit bronchoconstriction after bronchial allergen challenge was assessed in ten patients with a dual asthmatic response to inhaled allergen. The late allergic reaction was inhibited by a short pre-treatment (hours) while the immediate allergic reaction was reduced only after prolonged treatment (weeks), but it was possible to reduce also this reaction substantially. Three short-term studies, each involving eleven to twelve asthmatic patients, showed that inhaled budesonide had an anti-asthmatic effect that was dose-dependent and probably locally mediated. This therapeutic effect was also influenced by the dose-frequency. Budesonide was also used in two subacute studies in 18 and 34 patients respectively. Also these studies showed that budesonide had a dose-dependent anti-asthmatic effect. It was shown that an increased dose-frequency increased the therapeutic efficacy when asthma was in relapse but was of no importance in stable asthma. There was a good agreement between the results from the single-dose, the short-term and the subacute studies.			
Key words Budesonide - skin blanching - plasma cortisol - asthma - allergen challenge - dose-response			
Classification system and/or index terms (if any)			
Supplementary bibliographical information		Language English	
ISSN and key title		ISBN 91-86058-06-1	
Recipient's notes		Number of pages 148	
		Price	
		Security classification	
Distribution by (name and address)			

I, the undersigned, being the copyright owner of the abstract of the above-mentioned dissertation, hereby grant to all reference sources permission to publish and disseminate the abstract of the above-mentioned dissertation.

Signature



Date

1983 11 15

From the Department of Clinical Pharmacology
University of Lund
Sweden

Evaluation of Budesonide

- a new glucocorticosteroid
for local treatment of
bronchial asthma

by S-Å JOHANSSON

LUND 1983



ISBN 91-86058-06-1

 Rahms & Lund



Digitized by the Internet Archive
in 2026

https://archive.org/details/IA41546726_0028

Contents

	<u>page</u>
ABBREVIATIONS	3
PREFACE	4
INTRODUCTION	6
Proposed mechanism of action of glucocorticoids in bronchial asthma	6
Development of the therapy with inhaled glucocorti- coids in bronchial asthma	7
AIMS OF THE STUDIES	11
SUBJECTS, PATIENTS AND METHODS	12
Local anti-inflammatory potency	12
Systemic glucocorticoid potency	12
- oral administration study	12
- aerosol administration study	13
Effects on bronchial allergen challenge	13
Effect on bronchial asthma after short-term pre- treatment	14
Effect on bronchial asthma in subacute tests	15
- dose-response study	15
- dose-response and dose-frequency study	16
RESULTS AND DISCUSSION	19
Local anti-inflammatory potency as studied in the blanching test	19
Systemic glucocorticoid potency after oral dosing and inhalation, respectively	20
Effects on bronchial allergen challenge	23

Contents (continued)

page

Effect on bronchial asthma after short-term pre-treatment	24
- efficacy of inhaled and orally given budesonide	25
- dose-response study	27
- influence of administration frequency	28
Effect on bronchial asthma in subacute tests	32
- effect versus placebo	32
- dose-response relationship	34
- effect of dosing frequency	35
- side-effects	36
 GENERAL CONCLUSIONS	 37
Human pharmacology studies for glucocorticoid effect	37
Subacute clinical studies for anti-asthmatic effect	39
 ACKNOWLEDGEMENTS	 41
 REFERENCES	 42

Abbreviations

AUC	Area under curve
BDP	Beclomethasone dipropionate
BL	Baseline
BMP	Beclomethasone monopropionate
BUD	Budesonide
DSCG	Disodium cromoglycate
EC ₅₀	Concentration needed to give half maximum response
FEV _{1.0}	Forced expiratory volume in one second
GCS	Glucocorticosteroid(s)
MLPF	Mean low peak expiratory flow
NPD	Non-prednisone dependent
PD	Prednisone dependent
PEF	Peak expiratory flow
WBC	White blood cells

Preface

This thesis is based on the following papers, which will be referred to in the text by their Roman numerals:

- I Johansson SÅ, Andersson KE, Brattsand R, Gruvstad E, Hedner P: Topical and systemic glucocorticoid potencies of budesonide and beclomethasone dipropionate in man. *Eur J Clin Pharmacol* 22, 523-529, 1982.
- II Dahl R, Johansson SÅ: Importance of duration of treatment with inhaled budesonide on the immediate and late bronchial reaction. *Eur J Resp Dis Suppl* 122, 63, 167-175, 1982.
- III Ellul-Micallef R, Hansson E, Johansson SÅ: Budesonide: A new corticosteroid in bronchial asthma. *Eur J Resp Dis* 61, 167-173, 1980.
- IV Ellul-Micallef R, Johansson SÅ: Acute dose-response studies in bronchial asthma with a new corticosteroid, budesonide. *Br J Clin Pharmac* 15, 419-422, 1983.
- V Ellul-Micallef R, Johansson SÅ: Dose frequency in chronic bronchial asthma, with a new corticosteroid, budesonide. In manuscript.
- VI Johansson SÅ, Dahl R: A double-blind dose-response study of budesonide by inhalation in patients with bronchial asthma. Submitted for publication.

- VII Toogood JH, Baskerville JC, Jennings B, Lefcoe NM, Johansson SÅ: Influence of dosing frequency and schedule on the response of chronic asthmatics to the aerosol steroid, budesonide. J Allergy Clin Immunol 70, 4, 288-298, 1982.

Introduction

PROPOSED MECHANISM OF ACTION OF GLUCOCORTICOIDS (GCS) IN BRONCHIAL ASTHMA

The mode of action of glucocorticoids (GCS) in bronchial asthma is still incompletely understood. In in vitro studies it has, however, been shown that at least some of the actions of GCS are mediated via the synthesis of specific proteins. The initial steps in this process are that circulating GCS cross the cell membrane, enter the cell cytoplasm and attach to receptor proteins. This steroid/receptor complex then enters the cell nucleus. A messenger RNA is synthesized and transmits the information to the ribosomes on the endoplasmic reticulum which in turn generates specific proteins. One such protein termed lipomodulin and its active decomposition product macrocortin are reported to interact with phospholipase A_2 on the cell wall membrane and this causes a reduced production of leucotrienes and prostaglandins (Blackwell et al 1980, Hirata and Axelrod 1980), both considered to play an important role in asthma. Consequences of this indirect effect of GCS are a/ latency time for the action b/ the duration of action depends on both the half-life of the drug and of the active proteins c/ at the time of the therapeutic action there may be poor relationship between the plasma level of the drug and the effect.

At the start of the present work it was supposed that the main mechanism of GCS in asthma was just the anti-inflammatory effect (Claman 1975) and by this effect GCS reduce vascular permeability, edema, mucous secretion, infiltration and activation of inflammatory cells and all these effects are considered to be valuable

in the treatment of asthma. An other effect of potential value is that GCS restore a decreased number of β -receptors. For a review of the effects of GCS on the airways see Svedmyr (1982).

In parallel with the present work it has been shown that pre-treatment with GCS reduce the content of histamine in the nasal mucosa (Pipkorn and Andersson 1982), inhibit the IgE-mediated histamine release and bronchial anaphylaxis (Martin et al 1980, Andersson and Brattsand 1982, Pipkorn and Andersson 1982). How these latter mentioned effects are related to macrocortin and lipomodulin is not known.

DEVELOPMENT OF THE THERAPY WITH INHALED GLUCOCORTICOIDS IN BRONCHIAL ASTHMA

Addison was the first to describe the vital function of the adrenal glands (Addison 1855), but it was not until in the 1930's that adrenal extracts with reasonable activity could be tested (Swingle and Pfiffner 1930, Hartman et al 1930). During the 1940's there was a great interest in ACTH and corticosteroids and cortisol, cortisone and some other compounds were isolated 1942 (Reichstein and Shoppee 1942), and in 1944 Sarett succeeded in synthesizing cortisone (Sarett 1946). ACTH was reported on in asthma in 1949 (Bordley et al 1949), and in the same year cortisone was described in rheumatoid arthritis (Hench et al 1949), and a year later cortisone was also tried in asthma (Carryer et al 1950).

The initially encouraging results were soon accompanied by problems. Lowell and co-workers reported that out of 17 patients with asthma who had used cortisone for a year or more 10 had gained weight, six had rounding of the face and three had become hypertensive (Lowell et al 1953). In a group of 13 patients who were treated for 7 to 80 weeks, six put on weight, three became hypertensive and two died unexpectedly (Savidge and Brockbank 1954).

Soon after they had become available, the glucocorticosteroids were used to investigate if it was possible to obtain a local therapeutic effect after inhalation: cortisone acetate (Gelfand 1951), cortisol (Foulds et al 1955), prednisolone (Franklin et al 1958) were all tried, but it was not until self-propelled metered dose inhalers and corticosteroids with higher local potency became available that therapy with inhaled corticosteroids was investigated on a wider scale.

Dexamethasone as isonicotinate or phosphate became commercially available in some countries, but as it was well absorbed and had a long half-life in plasma (Swartz and Dluhy 1978) the aerosol treatment had no advantage to oral administration (Toogood, Lefcoe 1965). Betamethasone valerate in aerosol form is used in Great Britain and has been shown to have a therapeutic effect in the management of asthma (El-Shaboury and Williams 1974). Triamcinolone acetonide has been used in a number of clinical studies in the USA (Bernstein and Chervinsky 1982) but has not been made available to other patients than those participating in trials.

The most widely used inhaled corticosteroid is beclomethasone dipropionate (BDP) which was first tried in asthma in 1968. The first trials were no great therapeutic success and the drug was on the verge of being stopped for the treatment of asthma. However, some very successful studies were done by Brown and co-workers (Brown et al 1972). This work was followed by similar findings by other authors (e.g. Clark 1972, Lal et al 1972), and it soon became obvious that treatment of asthma with inhaled BDP was a powerful therapeutic tool that also had a low frequency of side-effects. (For a review of the development of the treatment with inhaled steroids, see Brown 1980.)

BDP inhalation therapy was first restricted to be used as substitution for oral GCS in a limited number of cases mainly because of fear of local atrophy of the bronchial mucous membrane. However, it has been shown that this does not seem to occur (Lundgren 1977, Thiringer et al 1977) and treatment with

BDP come into a widespread use. BDP was generally given in a rather low dose (about 400 µg/day) and it took several years from the publication of dose-response studies (Toogood et al 1977) before it was used in a more flexible way. Although being a major improvement in the therapy of asthma, BDP was still not an ideal compound and suppression of the adrenal system has been described (Mygind and Hansen 1973, Gaddie et al 1973, Toogood et al 1977, Wyatt et al 1978, Vaz et al 1982, Smith and Hodson 1983). For this reason the search for new and improved drugs has continued and budesonide is a result of this research.

Budesonide was first described in 1979 (Thalén and Brattsand 1979) and this drug has in animal models given a better ratio between topical and systemic effects than the reference drugs, BDP and triamcinolone acetonide (Brattsand et al 1982). The high local activity of budesonide is caused by the unsymmetric alkyl chain in the acetal group and the compound has been shown to have a very high GCS-receptor affinity (Dahlberg et al, in press) and this is the finding also in human lung (Hochhaus et al 1983).

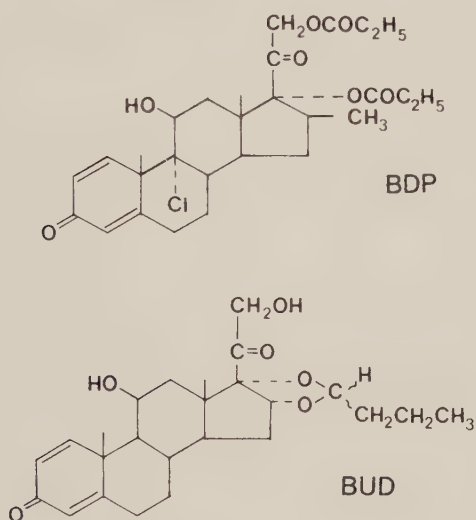


FIG 1. Structural formulas for BDP (beclomethasone, 17 α , 21, dipropionate) and budesonide (BUD) (16 α , 17 α , -butylidenedioxy-11 β , 21, dihydroxy-pregna 1,4-dione-3,20-dione)

The chemical differences between budesonide and BDP are shown in FIG 1. BDP is a 17 α , 21-diester with a chlorine-atom in the 9 α -position. It has a high topical activity as studied in the skin-blanching test but this activity is somewhat reduced after hydrolysis of the 21-propionate group and much more so after cleavage also of the 17 α -ester bond. After inhalation the first step occurs already in the lung, while the second probably takes place mainly in the liver. Budesonide is a 16 α , 17 α -acetal with an unsymmetrical alkyl chain and budesonide is not locally metabolized in the lung but extensively so in the liver. The first-pass metabolism after oral dosing is reported to be about 90% and the plasma half-life to $\approx$ 2h (Ryrfeldt et al 1982) and the formed metabolites have much less GCS activity (< 0.01) than budesonide (Dahlberg et al, in press). No figures on first-pass metabolism and half-life for BDP in plasma are available.

Other new corticosteroids that have been investigated by inhalation in asthma are flunisolide and fluorcortin butylester (FCB). Flunisolide has about 1/3 of the topical potency of budesonide (Johansson et al 1982) and about the same absolute systemic activity after both oral and aerosol administration (Johansson et al unpublished data) and it also has a definite effect in asthma (Lowell et al 1976).

FCB is reported not to be tested in asthma anymore, probably because of its low topical activity.

A possible explanation to why some of the substances have been in clinical phase for several years without being made available to the public may be that there are no generally accepted ways to investigate the therapeutic value of inhaled corticosteroids. Clinical investigations include a number of difficulties that are less prominent with e.g. bronchodilators (Björkander et al 1982). This means that it may be a troublesome and long process to define the relative value of a corticosteroid intended to be used by inhalation for the treatment of asthma.

Aims of the Studies

The aims of the studies have been to investigate:

- how budesonide compared to beclomethasone dipropionate (BDP) with respect to local anti-inflammatory and systemic effects (I).
- if inhaled budesonide could influence the immediate allergic reaction after a bronchial allergen challenge test (II).
- whether budesonide had a therapeutic effect after single dose or prolonged treatment in bronchial asthma and if so, also study the dose-response relationship for therapeutic effect (III, IV, VI, VII).
- the importance of the administration frequency (V, VII).
- if the results from selected trials with short-term treatment could predict the outcome of more prolonged clinical trials in asthma (I-VII).

Subjects, Patients and Methods

LOCAL ANTI-INFLAMMATORY POTENCY (I)

Twelve healthy volunteers participated in a first and 10 in a second study. Thirty-two test sites, 7x7 mm each, were marked with silicone grease on the forearms and 10 μ l of a test solution was administered to each square. The arms were covered with plastic film when the diluent (ethanol) had evaporated. The cover was removed after 18 hours and the arms were washed with ethanol and then the blanching was estimated according to a four graded scale 1, 2, 3, 4, 6, 12 and 24 hours after the plastic film had been removed. Time-effect curves were constructed for all substances and doses and the relative potency values were calculated.

SYSTEMIC GLUCOCORTICOID POTENCY (I)

Oral administration study

Eight healthy volunteers took part in the study. The effects of 2, 4 and 8 mg of BDP and budesonide on plasma cortisol, total and differential white blood cells (WBC) were tested. The drugs were micronized and given in gelatine capsules. The placebo capsules were filled with lactose only. For investigation of each drug and dose two consecutive days were used, and day I was always the placebo day. This was done in order to avoid any residual effects from the test drugs on the placebo values.

The test drugs were given in the evening at 10 p.m. on the day before investigation. On trial days the subjects came to the clinic at 8 and 10 a.m. and at noon. A venous blood sample was taken at each occasion and total and differential white blood cell count (WBC) was made with a Coulter Counter and by counting 500 cells. Plasma was prepared and stored at -20°C until analyzed for cortisol by radio-immunoassay.

Aerosol administration study

Twelve volunteers participated in this study. The time schedule was as described for the "Oral administration study". The participants were trained to use a metered dose inhaler. The tested doses were for BDP 200, 800 and 3250 μg and for budesonide* 200, 800 and 3200 μg . For both drugs conventional actuators were used.

All studies were performed as double-blind with regard to active treatments and the drugs were given at random.

EFFECTS ON BRONCHIAL ALLERGEN CHALLENGE (II)

Ten patients with dual bronchial response to allergen inhalation took part in each of two open studies. The allergen dose needed to decrease PEF by 15-40% within 30 minutes after challenge was individually titrated before the onset of the studies. Both studies started with a control provocation to confirm the dose and the dual response. All patients had mild asthma and did well without asthma-medication except bronchodilator aerosols which were allowed for occasional use but not later than eight hours before a test.

* Pulmicort^R, Spirocort^R, AB DRACO, Lund, Sweden

Study one

One week after the control-test the patients returned for a repeat challenge. They had then inhaled 1 mg of budesonide on the previous day at 8 p.m. and 1 mg in the morning four hours before the challenge. After the challenge the patients continued to inhale budesonide 1 mg/day (400 µg in the morning and 600 µg in the evening) for seven days and then returned for a third challenge. Also at this occasion they inhaled 1 mg budesonide four hours before the test.

Study two

After the control challenge, the patients continued budesonide 1 mg/day in the same way as in the previous study for four weeks returning for repeat challenges after one and four weeks. As in study one, 1 mg of budesonide was given four hours before each test.

In both studies lung function was followed by frequent measurements of PEF for at least eight hours after the challenge.

EFFECT ON BRONCHIAL ASTHMA AFTER SHORT-TERM PRE-TREATMENT
(III, IV, V)

Twelve patients suffering from chronic bronchial asthma took part in each study. Chronic asthma was defined as a condition in which reversible airflow obstruction was present for a prolonged period of time with or without brief spontaneous remissions. FEV₁ in % of predicted normal values and increase in FEV₁ after two inhalations from a bronchodilator aerosol are shown in TABLE 1.

Study no	FEV ₁ in % of predicted normal value. Mean (range)	Increase in FEV ₁ % 15 min after in- halation of broncho- dilator Mean (range)
III. a/ Pred. p.o. - bud. inh.	67 (59 - 73)	20 (16 - 26)
b/ Placebo p.o. - bud. p.o.	68 (57 - 79)	23 (12 - 38)
IV.	71 (65 - 79)	23 (13 - 56)
V.	64 (56 - 74)	20 (15 - 30)

TABLE 1. Mean (range) FEV₁ in % before and after inhaled broncho-dilator

The patients were carefully followed also before the studies and were known to show small diurnal and day-to-day variations in their PEF measurements.

Each study started at 8 a.m. and the effect of each treatment was followed by hourly PEF-readings for 12 hours. Before the onset of a study the patients were trained to use a peak flow-meter and how to inhale from a metered dose inhaler. All studies were performed as double-blind cross-over studies and all treatments were given in randomized order. However in study III b placebo versus budesonide p.o. was single-blind and the treatments were given in fixed order.

EFFECT ON BRONCHIAL ASTHMA IN SUBACUTE TESTS (VI, VII)

Dose-response study (VI)

The study was performed in 18 adults suffering from chronic bronchial asthma not sufficiently controlled by the use of bronchodilators and DSCG, but needing additional medical treatment as well. Each treatment was given for two weeks and the

investigated budesonide doses were 25, 100 and 400 μg , all given q.i.d. which means that the total daily doses were 100, 400 and 1600 μg , respectively. Budesonide was given from a pressurized aerosol provided with a conventional actuator and the effect of the treatments was followed by twice daily registration of PEF, symptom score and bronchodilator use.

The study was performed using cross-over technique and with randomized order between the active treatments, starting with a run-in period of at least one week's duration and ending with two weeks on placebo. The investigation was double-blind with respect to the active treatments, but the investigators knew that the last period was a placebo-period.

Dose-response and dose-frequency study (VII)

Thirty-four patients suffering from chronic asthma took part in the study. They had all benefited from earlier BDP treatment. 19 regularly used oral prednisone on alternate mornings. The study was a balanced cross-over, comparing two dose frequencies (b.i.d. and q.i.d.) at three dose levels of budesonide (400, 800 or 1600 $\mu\text{g}/\text{day}$) given by two dosing schedules (a.m. or a.m./p.m.). Every treatment was given for two weeks. Budesonide was inhaled from a pressurized aerosol via a conventional actuator. For trial design see FIG 2.

TRIAL DESIGN

PD/NPD

	BL ₁	4 doses/d AM-PM	4 doses/d AM	BL ₂	2 doses/d AM	2 doses/d AM-PM
Run-in		0.4 0.8 1.6	1.6 0.8 0.4		0.4 0.8 1.6	1.6 0.8 0.4

5/4

Daily dose of
budesonide

	BL ₁	4 doses/d AM	4 doses/d AM-PM	BL ₂	2 doses/d AM-PM	2 doses/d AM
Run-in		0.4 0.8 1.6	1.6 0.8 0.4		0.4 0.8 1.6	1.6 0.8 0.4

4/4

Daily dose of
budesonide

	BL ₁	2 doses/d AM	2 doses/d AM-PM	BL ₂	4 doses/d AM-PM	4 doses/d AM
Run-in		0.4 0.8 1.6	1.6 0.8 0.4		0.4 0.8 1.6	1.6 0.8 0.4

5/4

Daily dose of
budesonide

	BL ₁	2 doses/d AM-PM	2 doses/d AM	BL ₂	4 doses/d AM	4 doses/d AM-PM
Run-in		0.4 0.8 1.6	1.6 0.8 0.4		0.4 0.8 1.6	1.6 0.8 0.4

5/3

Daily dose of
budesonide

Accumulated number
of weeks

0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30
---	---	---	---	---	----	----	----	----	----	----	----	----	----	----	----

The number of prednisone dependent (PD) and non-dependent patients (NPD) in each group is shown to the right and the number of accumulated weeks in the trial at the bottom line. Inhaled steroids were substituted with placebo in BL₁, and during BL₂ 400 µg BDP was given daily.

PEF was recorded twice daily at home, and diary cards for use of medication were filled in. The effect of each treatment was independently scored both by the physician and the patient. Spirometric measurements were performed at the clinic at the end of every single period and blood was sampled at 8 a.m. for estimation of cortisol levels.

Results and Discussion

LOCAL ANTI-INFLAMMATORY POTENCY AS STUDIED IN THE BLANCHING TEST (I)

The local or "topical" anti-inflammatory effect in the lung is thought to be a main mechanism of action of an inhaled GCS in the treatment of asthma. There are no relevant models for determination of topical anti-inflammatory effect in the lung. Therefore, we decided to use the topical anti-inflammatory potency expressed as the ability to induce skin blanching in human volunteers. This has been suggested by Harris (1980) as a suitable first step in assessing the properties of a GCS intended to be used by inhalation for the treatment of asthma.

The relation between the anti-inflammatory and blanching effects is not known, but it has been shown that GCS can inhibit increase in vascular permeability without effecting the blood content of a tissue (Sugio and Tsurufuji 1981) and it is possible that skin blanching is secondary to a shift in blood flow rather than a primary effect (Kristensen et al 1977).

To be of potential value for the treatment of asthma a drug in this test model should probably have a high potency as only small amounts can be given by inhalation.

The test result showed that budesonide had a higher topical potency than the other compounds tested, including BDP.

TABLE 2.

TABLE 2. Skin-blanching: results of Test I (I)

Glucocorticoid	EC ₅₀ (μ g/ml)	95% confidence interval	Rel. potency (area under curves)
Dexamethasone			
isonicotinate	19.1	53.8-11.0	0.02
Triamcinolone acetonide	6.1	10.8- 3.6	0.2
Beclomethasone			
dipropionate	3.1	5.3- 1.9	0.3
Fluocinolone acetonide	3.1	6.4- 1.8	0.5
Betamethasone valerate	2.1	4.2- 1.2	0.3
Budesonide	1.0	1.5- 0.6	1

The comparison between budesonide and BDP was repeated in a second test and showed the same relationship between the drugs, although their absolute potencies were somewhat different.

At a later stage the tests were further extended and the results showed that budesonide had about twice the local anti-inflammatory potency of BDP (Johansson et al 1982).

SYSTEMIC GLUCOCORTICOID POTENCY AFTER ORAL DOSING AND INHALATION, RESPECTIVELY (I)

In order to avoid unwanted long-term systemic effects a desirable property of a GCS intended to be used by inhalation is that it should have a low systemic activity within the therapeutic dose range. The systemic potency can be studied as the ability to suppress the plasma cortisol level and to change the number and proportion of the white blood cells.

When budesonide and BDP were compared by oral route, BDP showed a higher potency in inducing systemic effects. The effect on plasma cortisol is shown in FIG 3.

PLASMA CORTISOL (AUC) ORAL DOSING N=8

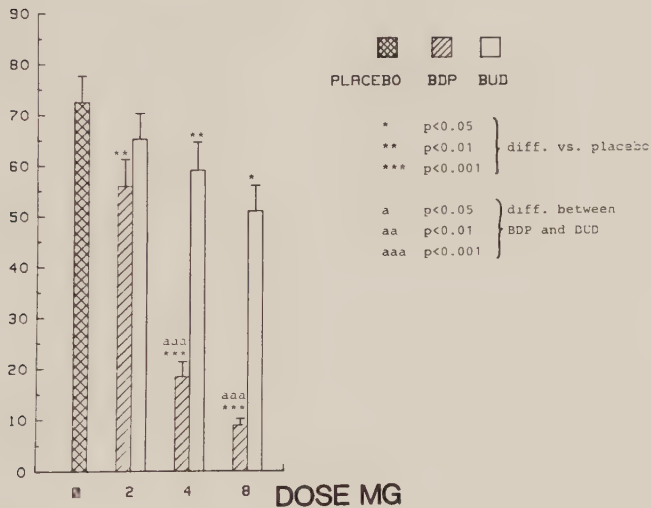


FIG 3. Area under curve (AUC) for plasma cortisol after placebo, BDP and budesonide by mouth ($M \pm SEM$, $n = 8$)

When the drugs were compared by inhalation, the results still showed BDP to be a more potent inducer of the measured systemic effects. FIG 4.

PLASMA CORTISOL (AUC) INHALATION N-12

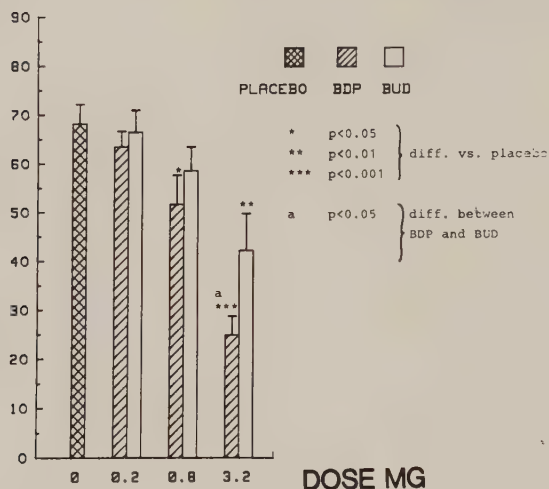


FIG 4. Area under curve (AUC) for plasma cortisol after inhalation of placebo, BDP and budesonide ($M \pm SEM$, $n = 12$)

Complete dose-response curves for BDP and budesonide after inhalation for the effect on plasma cortisol have now been constructed by other groups (Löfdahl et al 1983), confirming that budesonide has about half the systemic potency compared to BDP.

The explanation why budesonide has both a high topical and a low systemic potency is that the drug has a high GCS-receptor affinity (Hochhaus et al 1983) combined with a high first-pass metabolism and therefore a short half-life after absorption (Ryrfeldt et al 1982). No comparable data are known for BDP but in an in vitro biotransformation system BMP (the main active principle in BDP) has a 2-4 times longer half-life than budesonide (Ryrfeldt et al 1982).

The conclusion from the above mentioned results is that budesonide has an improved pharmacological profile and that it according to the test models used, shows a better separation between local and systemic GCS-effects compared to BDP. These results are in accordance with the results from experimental work in animals (Brattsand et al 1982).

EFFECTS ON BRONCHIAL ALLERGEN CHALLENGE (II)

It has been well established that pre-treatment with GCS decreases or abolishes the late allergic bronchial reaction (Booij-Noord et al 1972), and most authors have reported no effect on the immediate bronchial reaction (Booij-Noord et al 1971, Pepys 1975) although positive reports are not totally missing (Martin et al 1980, Burge et al 1982).

Our study confirmed that a short pre-treatment had markedly reduced the late bronchial reaction but did not significantly affect the immediate reaction. In addition we found that a prolonged treatment with an inhaled GCS had a very good ability to decrease also the immediate bronchial reaction. FIG 5.



FIG 5. PEF (l/min) from 0 to 8 hours after control challenge and after pre-treatment with budesonide for one and four weeks ($M \pm SEM$, $n = 10$)

This inhibitory effect on the immediate bronchial reaction is in agreement with a parallel result by Burge et al (1982). They found that prolonged treatment with inhaled BDP could reduce the immediate allergic bronchial reaction after challenge. The findings are further supported by experimental work where it has been shown that budesonide for a week reduced both the histamine content and the IgE-mediated histamine release from nasal mucosa (Pipkorn and Andersson 1982). The long pre-treatment time needed for inhibition of immediate allergic reactions in the lung and in the nose may suggest that in these organs GCS act by inhibiting cell infiltration, mediator storage and/or by decreasing the activity of the IgE-binding factors (Yodoi et al 1981).

The mechanism behind the inhibition of the late bronchial reaction is not known, but there is a good agreement between the short latency time for this effect and the latency time for inhibition of e.g. increased capillar permeability (Svensjö 1983) and lung edema formation (Brattsand et al 1983). A short latency time agrees better with the time needed for synthesis of the GCS-induced specific proteins (Chan and O'Malley 1978).

The conclusion from the study is that inhaled budesonide has the ability to reduce or inhibit both the immediate and late allergic bronchial reaction provided the pre-treatment time has been long enough. The therapeutic value of the prophylactic effect needs to be further investigated, but it has been shown to be present also at lower dose-levels (Kiviloog et al 1982). Furthermore it has been shown that inhaled budesonide is effective also in inhibiting exercise-induced asthma in children (Henriksen et al 1982).

EFFECTS ON BRONCHIAL ASTHMA AFTER SHORT-TERM PRE-TREATMENT (III, IV, V)

Investigations on the acute effect of GCS in bronchial asthma have been performed by a number of investigators and already in 1956, the Medical Research Council in Great Britain concluded

that they were useful in acute asthma. Later work has also confirmed that it is possible to obtain improvement in pulmonary function some hours after a single dose of a GCS (Ellul-Micallef and Fenech 1975, Klaustermeyer and Hale 1976, Dugue et al 1977, Dahl and Johansson 1982^a). However some authors still deny the acute therapeutic effect of GCS in bronchial asthma (e.g. McFadden et al 1976, Luksza 1981).

A possible explanation for these contradictory findings could be that the components, bronchoconstriction, mucous secretion and inflammation are present in various proportions among patients presenting with bronchial asthma. In those who respond, the improvement in pulmonary function have a time course of response that is similar to the time course for other effects of GCS, e.g. anti-edematous effect (Svensjö 1983), effect on blood glucose (Walton et al 1970) and the effect on leucocytes (Mishler 1977). For this reason it seems likely that the rapid improvement in pulmonary function after a GCS in these patients is mediated via anti-inflammatory mechanisms. In patients who do not improve after a single dose or a short course of GCS the inflammation may still be a prominent factor although complicated by others (Gibson 1983). The effectiveness of a GCS can not be out-ruled before a high enough dose (≈ 40 mg prednisolone/day) has been tested for at least two weeks (Cochrane 1983).

When we started our first study there was no information available regarding inhaled GCS and rapid improvement in pulmonary function. If such a test model turned out to be successful it might mean that it could be used as a human model for future investigations of anti-asthmatic effects of GCS.

Efficacy of inhaled and orally given budesonide (III)

The study showed a marked improvement in pulmonary function after prednisolone 40 mg by mouth and budesonide 1 mg by inhalation. FIG 6. When a corresponding budesonide dose was given by oral route there was little or no effect. FIG 7.

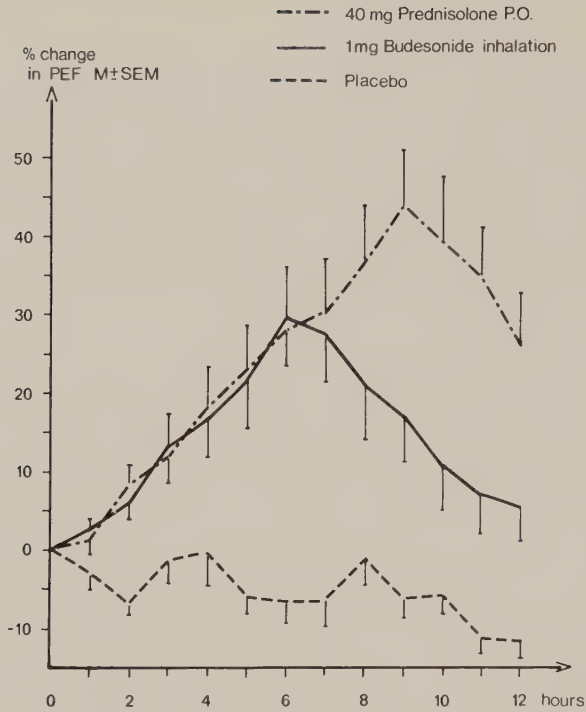


FIG 6. Effect on PEF of a single oral dose of prednisolone, budesonide by inhalation and placebo ($M \pm SEM$, $n = 12$)

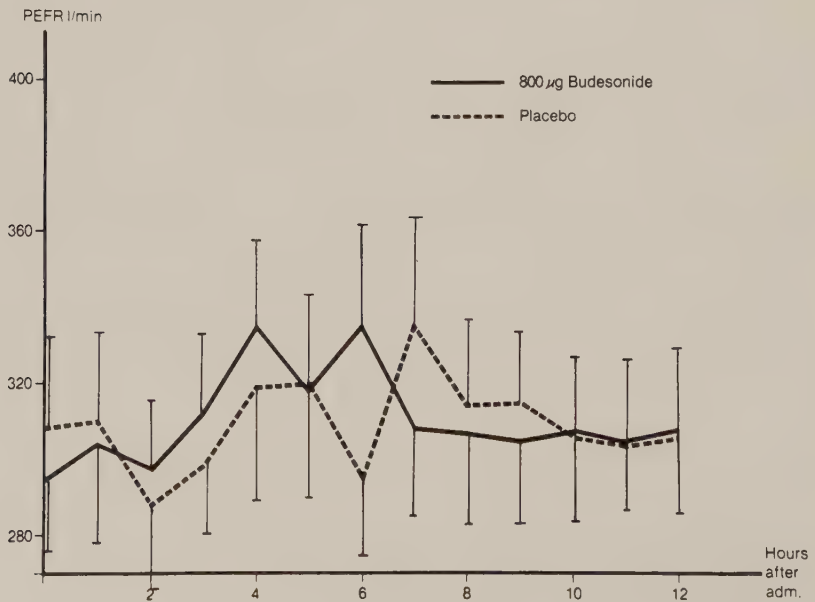


FIG 7. Effect on PEF of a single oral dose of budesonide and placebo ($M \pm SEM$, $n = 12$)

Both local and systemic therapy had the same short latency after inhalation and the increase in PEF was the same from 0-6 hours. The increase in PEF-values continued for about three hours longer with prednisolone than with inhaled budesonide.

Dose-response study (IV)

All inhaled doses of budesonide (100, 400 and 1600 μ g) and prednisolone 40 mg by mouth gave similar effects on pulmonary function for the first five hours. This indicates that the threshold dose for inhaled budesonide is ≤ 100 μ g and that once the effect has been triggered it will last for about 5 hours.

FIG 8.

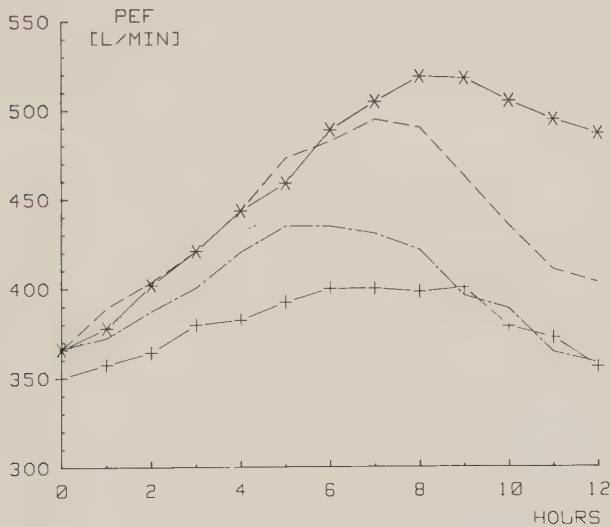


FIG 8. Time course of response to oral prednisolone and budesonide in one oral and three inhaled doses (M, n = 12)

--	prednisolone 40 mg p.o.	} by inhalation
----	budesonide 1600 μ g	
.....	budesonide 400 μ g	
.-.-.	budesonide 100 μ g	
+--+	budesonide 1600 μ g p.o.	

The investigation also showed that there was a good linear relationship between the AUC for PEF and log dose of budesonide. FIG 9.

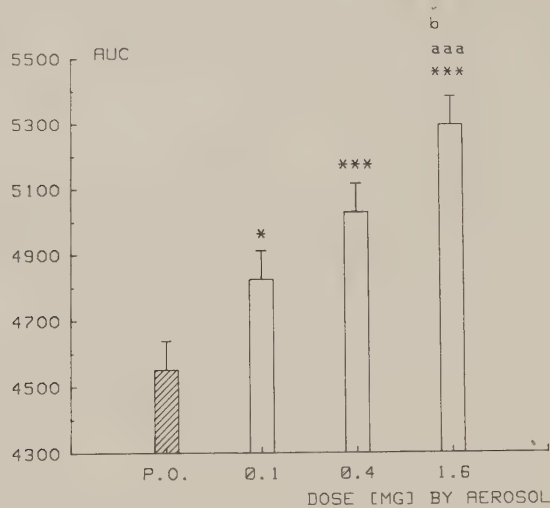


FIG 9. Area under curve (AUC) calculated on PEF for one oral and three inhaled doses of budesonide ($M \pm SEM$, $n = 12$)

*	$p < 0.05$	} Difference vs budesonide 1.6 mg p.o.
***	$p < 0.001$	
aaa	$p < 0.001$	Difference vs budesonide 0.1 mg by inhalation
b	$p < 0.05$	Difference vs budesonide 0.4 mg by inhalation

The longer duration and higher AUC for PEF for higher doses of inhaled budesonide may be partly explained by prolonged presence of budesonide in the lungs.

This trial did not tell whether or not budesonide 1.6 mg by mouth had a significant effect on lung function as no placebo-day was used.

The bioavailability of budesonide has been investigated by Ryrfeldt et al (1982). They found it to be 11% after oral dosing and after inhalation through an extended mouthpiece (Inhalet^R) the corresponding figure was about 70%. The figure for availability after inhalation is corrected for what was washed out of the oral cavity and what had been deposited in the aerosol device.

The sum of these two non-respired fractions were 35% of the given dose. This means that in this experiment the bioavailability of the nominal dose was close to 50%. This is an extremely high figure for bioavailability of inhaled drugs and the figure is generally thought to be about 10% (Davies 1978).

Information about therapeutic efficacy and bioavailability can be combined to estimate if inhaled budesonide acts "locally" in the lung or by the proportion available to the systemic circulation. If the systemic bioavailability was the most important factor, the therapeutic effect of 1600 µg orally (~170 µg systemically bioavailable) should have been greater than that after inhalation of 100 µg (~50 µg systemically bioavailable). The effect of 1600 µg by oral route was however much less than should have been expected from data on bioavailability and corresponded to a theoretical inhaled dose of 25 µg (bioavailability < 15 µg). This discrepancy by a factor 10 could be understood if the effects of inhaled budesonide were essentially mediated locally in the lung.

Influence of administration frequency (V)

This investigation showed that dosing frequency can have an important effect on the relief of airflow obstruction as 4 x 100 µg given with 2h interval had a higher peak effect and longer duration than 1 x 400 µg and with regard to duration 4 x 100 µg was also superior to 1 x 1600 µg. FIG 10.

The difference between the treatments would probably have been greater if it had been possible to give the divided doses more than 2 hours apart. The trial could however not be prolonged beyond 12 hours and as we wanted that also the effect of the last part of the dose should reach its maximum before the end of the trial we decided to have two hours between the divided doses.

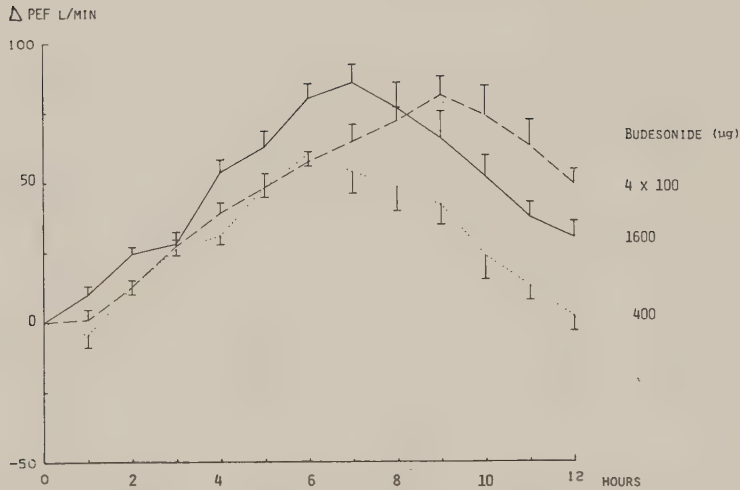


FIG 10. Change in PEF after treatment with budesonide ($M \pm SEM$, $n = 11$)

The single dose of 400 µg seemed to have a rather long duration (IV, V) and the data supports that in practice a dosing interval of 8 to 12 hours would be relevant.

The conclusions from the studies (III-V) are that:

- inhaled budesonide can give a rapid improvement in pulmonary function in suitable patients, whereas budesonide by oral route was without such an effect. (III)
- the threshold dose for effect after inhalation was ≤ 100 µg (IV)

- when the effect had been triggered by budesonide it lasted for about 4-6 hours. (III-V)
- split doses gave a more pronounced and longlasting increase in pulmonary function than a single dose. (V)
- budesonide acts locally in the lung. (IV)
- this acute model is sensitive and suitable for the testing of anti-asthmatic efficacy of GCS. A single dose is sufficient and by this only short-term toxicity studies would be necessary as underlying toxicological documentation. (III-V)

EFFECT ON BRONCHIAL ASTHMA IN SUBACUTE TESTS
(VI, VII)

Very few dose-response trials have been performed with inhaled BDP. In one of them no dose-response relationship was demonstrated (Gaddie et al 1973) whereas in others a high dose gave a better effect than a low (Clark et al 1975, Toogood et al 1977). It is however hard to draw firm conclusions from these trials, as the dose in all of them was progressively larger. For this reason it is not possible to clearly differentiate between the effect of extended treatment time and the effect of an increase in dose.

In a previous paper (Björkander et al 1982), we have described some alternative trial designs for the assessment of a GCS in bronchial asthma. We found that one should avoid to randomize a placebo-period into the trial but rather place it at the end of the trial. In this way residual effects of placebo in a succeeding test period could be avoided as well as drop-outs due to relapse in asthma during placebo.

Based on the above mentioned findings two different dose-response studies were performed. One of the investigations was designed with random order between the different dose-levels and placebo was used at the end of the trial (VI). In the other study (VII) placebo was used at the start and the doses were given in a fixed order. FIG 2. In the latter study drop-outs during the placebo period were prevented by increasing the dose of oral GCS.

Effect versus placebo (VI, VII)

The evening values in PEF were significantly above the placebo value at budesonide doses ≥ 400 $\mu\text{g/day}$ (VI). In absolute terms the difference was however not impressing and contributing reasons for this are:

- a/ that there was high drop-out frequency during placebo. FIG 11. As a consequence it was impossible to obtain a PEF value that was representative for the effect of placebo.
- b/ that the consumption of inhaled bronchodilators tended to increase during the placebo period.

The therapeutic effect of budesonide was better demonstrated by the drop-out rate during the various treatment periods. There were no drop-outs while on budesonide 400 or 1600 $\mu\text{g}/\text{day}$. Two patients dropped out while on 100 $\mu\text{g}/\text{day}$ (their last treatment period) and further 10 during the placebo. FIG 11.

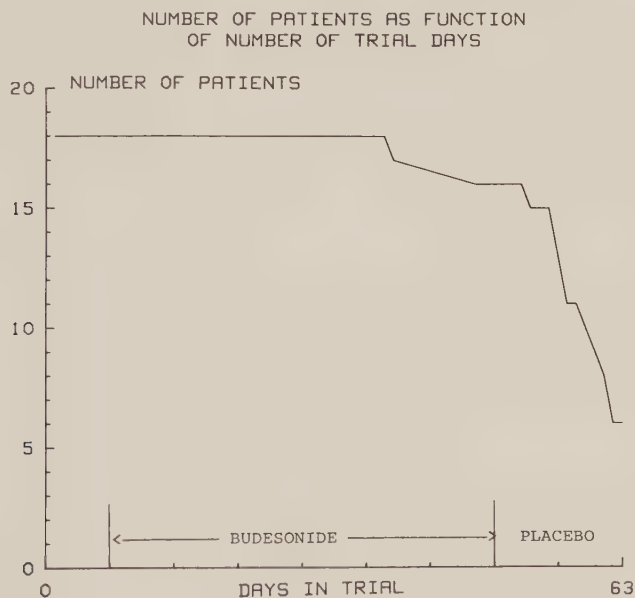


FIG 11. Number of patients in the study (VI) while on active treatment and placebo.

In study VII drop-out was prevented by increasing the dose of oral prednisone in the first placebo period as it was found that placebo caused an un-acceptable degree and frequency of complications. During what was planned to be a second placebo period budesonide was substituted with BDP aerosols. The consequence was that neither from this study can a quantitative comparison between budesonide and placebo be made.

Dose-response relationship in asthma (VI, VII)

Three doses of budesonide were tested in both studies and the slopes for the obtained regression lines were similar both within and between studies, within the investigated dose-range (100-1600 $\mu\text{g}/\text{day}$). These findings are in agreement with the results from the single dose study (IV). It has recently been shown that the linearity was present, still at 3.2 mg/day (Toogood et al 1983). The absolute levels differed, depending on the participating patients. FIG 12.

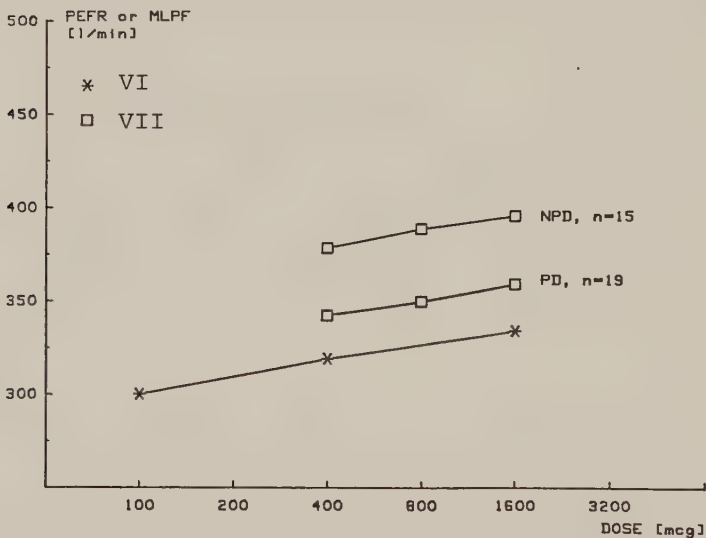


FIG 12. Dose-response curves for peak expiratory flow after different doses of inhaled budesonide

PD = prednisone dependent patients

NPD = non-prednisone dependent patients

Regarding the symptom score, the dose response was obvious in study VII but less so in study VI. However, in this study (VI) the patients decreased their highest dose from 1600 $\mu\text{g}/\text{day}$ to about 1200 $\mu\text{g}/\text{day}$ and tended to increase the lowest (+ 10%). These spontaneous changes may be interpreted as a dose-response relationship as they occurred in spite of the trial being double-

blind. This spontaneous decrease in dose was not seen in study VII and may reflect that the patients in this study were more familiar with the test situation.

Although studies VI and VII differed in investigated dose levels, randomized versus fixed order of dose-levels, location of placebo and selected patients they gave similar information regarding the dose-response relationship.

As a consequence of the linearity for the dose-response curve within the wide dose range it would be justified to increase the dose when a better effect is desired as such an increase is likely to give an improved clinical effect. It ought to be equally natural to decrease the dose once the asthma is under control so that each patient is maintained on his/her minimum effective dose.

Effect of dosing frequency (VII)

When the two dose-frequencies were compared it was found that a more frequent dosing was of importance when asthma was in relapse but had no major influence when asthma was in remission.

FIG 13.

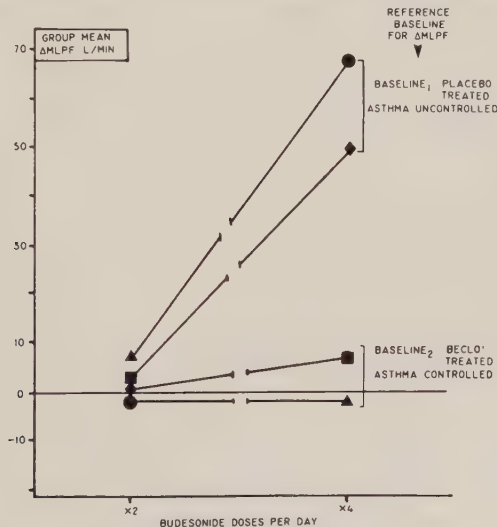


FIG 13. Influence of dosing frequency of asthma in relapse and in remission.

The findings are in agreement with those of Munch et al (1982) who showed that dose-frequency was of no major importance when the length of the trial was four weeks and when patients with stable asthma had been selected for the trial. On the other hand dose-frequency was a discriminating factor in another trial when stability in asthma was not an inclusion criterion (Dahl and Johansson 1982^b). It should also be noted that dose frequency had a clear effect on pulmonary function in a short-term study (V).

Side-effects (VI, VII)

The frequency of subjectively reported side-effects was low but some patients had a husky voice (VII). Regarding the systemic effects these were only assessed in study VII and the data showed that they were also dose-dependent. For non-prednisone dependent patients the reduction in plasma cortisol levels reached statistical significance when the dose was 1600 µg/day. Also in the prednisone dependent patients there was a dose-response relationship. Among those patients the reduction was statistically significant at 800 µg/day reflecting their greater load of GCS. The findings on frequency and severity of side-effects are in agreement with those from other studies (Björkander et al 1982, Rosenhall et al 1982, Willey et al 1982).

Conclusions from studies VI and VII:

- there was a dose-response relationship for inhaled budesonide within a wide dose-range.
- this could be demonstrated with both trial designs and in both prednisone dependent and non-prednisone dependent patients
- the difference between the two dose frequencies was most pronounced when asthma was in relapse but very much less so when in remission. Increasing the dose frequency may be of major importance for the effect of the treatment.

General Conclusions

HUMAN PHARMACOLOGY STUDIES FOR GLUCOCORTICOID EFFECT

Systemic glucocorticoid actions

- Based on depression of plasma cortisol it was found that inhaled budesonide had about half the systemic glucocorticoid potency of BDP (I). After oral dosing the difference between the drugs was even greater. (I).

Proposed anti-asthmatic actions

- The high local (topical) potency of budesonide observed in the skin blanching test (I) corresponded to a high anti-asthmatic potency of inhaled budesonide and a single dose of 100 µg was sufficient for a significant acute effect (IV). This supports the proposal by Harris (1980), that the skin-blanching test is a good early model for testing of GCS intended to be used in asthma.
- In chronic stable asthmatics inhaled budesonide in doses ≥ 100 µg improved the pulmonary function after a latency time of 2 hours (III, IV, V). There was a dose-response relationship when e.g. the AUC for PEF was calculated for the first 12 hours (IV). As this test model seems to be sensitive and reliable it can be used for early determination of anti-asthmatic potency of new GCS.

- Based on calculations on the bioavailability it was concluded that the anti-asthmatic effects of inhaled budesonide are mediated by local mechanisms rather than by systemic (III, IV).
- Inhaled budesonide could inhibit the bronchoconstriction after the late and the immediate allergic bronchial reaction, "anti-anaphylactic activity" (II). The pre-treatment times needed to inhibit the bronchospasm after these two reactions were different. For the late reaction a few hours were sufficient but for the immediate reaction the pre-treatment time had to be ≥ 1 week. The difference between the lengths of the pre-treatments, indicates that the effects of GCS on immediate and late reactions are mediated by different mechanisms.
- The inhibition of the late allergic bronchospasm is probably related to the anti-inflammatory activity, as these two effects have a similar time course. The underlying mechanism for the inhibition of the immediate allergic bronchospasm is more obscure. It probably depends on inhibition of the mediator release, but it is not known why the pre-treatment time has to be much longer than for the late allergic reaction.
- To be of potential clinical value a GCS should probably have both anti-inflammatory and anti-anaphylactic activity. Both these effects can be investigated by bronchial allergen challenge by varying the length of the pre-treatment period.
- The mechanism behind the improvement in pulmonary function in the short term tests (III-V) is not known, but it has a similar time course as that of the anti-inflammatory effect (a few hours).

Suitability of the selected test models

- The selected test models can be used step-wise and the toxicological documentation can be increased accordingly. Local anti-inflammatory potency can be estimated early in the skin blanching test and with a minimum of work for drug formulation. When a formulation for inhalation is available anti-asthmatic (anti-inflammatory?) activity can be investigated in short term studies (II-V). For the testing of anti-anaphylactic effect on the other hand, longer treatment periods are needed (II) and for this kind of investigations an much extended toxicological documentation is required.

SUBACUTE CLINICAL STUDIES FOR ANTI-ASTHMATIC EFFECT

Trial methodology

- For ethical reasons it is not possible to perform a strict comparison between an inhaled GCS and placebo. However, in the selected subacute test models it will be possible to perform comparisons between doses and/or drugs. It is however desirable to include a placebo period at the end of the trial to get information on whether the patients in the trial could have benefitted from the test drugs. This information is essential particularly in a situation where no difference has been observed between two or more treatments. The placebo period should be of the same length as the other test periods, but the patients should be switched to active treatment when they start to deteriorate, and the only purpose of this period is to check the GCS-dependency for the patients included in the study. Another way of doing this is to have a run-in period on a high dose of a GCS before the onset of a trial and include only those patients who have a predetermined positive response.

Results with the selected trial designs

- Prolonged treatment with budesonide did not result in more pronounced systemic effects than were observed after a single dose at 10 p.m. (VII, I).
- A dose-response relationship was established over a wide dose-range for the anti-asthmatic effect of inhaled budesonide. Similar information was obtained from studies with different designs. (VI, VII).

Therapeutic implications

- With sufficient duration of the pre-treatment, budesonide can be considered a prophylactic (anti-anaphylactic) agent.
- Increase in dose frequency is likely to have a beneficial therapeutic effect.
- To give optimum benefit to a patient the dose should be individualized, and an increase in dose can be justified as budesonide has an improved separation between local and systemic effects.

Acknowledgements

I wish to express my sincere gratitude to my friends and colleagues and I am particularly indebted to:

- Professor Karl-Erik Andersson who generously placed facilities at my disposal and for valuable help, discussions and encouragement
- Associate Professor Ralph Brattsand for introducing me into the field of research and for invaluable support, encouragement and criticism
- Associate Professors Ronald Dahl, Roger Ellul-Micallef and Professor John H Toogood for their deep knowledge and interest in research but especially for their personal warmth
- Associate Professor Pavo Hedner for a long and fruitful co-operation

I am also indebted to:

- Associate Professor Eskil Hansson for inspiring me to start this work
- Registered nurse Stina Ragnarsson, Laboratory assistants Anna-Britta Eriksson and Gertrud Lundqvist for their skillful assistance and positive interest
- Miss Maria Wallin for excellent secretarial help
- Miss Yvonne Lundsholm for revising the English text

Above all I am grateful for the patience and support from my wife Anita and our children Anna, Albert and Fredrik.

References

Addison T: On the constitutional and local effects of diseases of the suprarenal capsules. Samuel Higley, London 1855.

Andersson P, Brattsand R: Protective effects of the glucocorticoid, budesonide, on lung anaphylaxis in actively sensitized guinea-pigs: inhibition of IgE - but not IgG-mediated anaphylaxis. *Br J Pharmac* 76, 139-147, 1982.

Bernstein IL, Chervinsky P: Efficacy and safety of triamcinolone acetonide aerosol in chronic asthma. *Chest* 81, 20-26, 1982.

Björkander J, Formgren H, Johansson SÅ, Millqvist E: Methodological aspects on clinical trials with inhaled corticosteroids: Results of two comparisons between two steroid aerosols in patients with asthma. *Eur J Resp Dis Suppl* 122, 63, 108-117, 1982.

Blackwell GJ, Carnuccio R, DiRosa M, Flower RJ, Parente L, Persico P: Macro cortin: a polypeptide causing the anti-phospholipase effect of glucocorticoids. *Nature* 287, 147-149, 1980.

Booij-Noord H, Orie NGM, deVries K: Immediate and late bronchial obstructive reactions to inhalation of house dust and protective effects of disodium cromoglycate and prednisolone. *J Allergy Clin Immunol* 48, 344-354, 1971.

Booij-Noord H, deVries K, Sluiter HJ, Orie NGM: Late bronchial obstructive reaction to experimental inhalation of house dust extract. Clin Allergy 2, 43-61, 1972.

Bordley JE, Carey RA, McGehee-Harvey, Howard JE, Kattus AA, Newman EV, Winkenwerder WL: Preliminary observations on the effect of adrenocorticotrophic hormone (ACTH) in allergic diseases. Bull Johns Hopk Hosp 85, 396-398, 1949.

Brattsand R, Thalén A, Roempke K, Källström L, Gruvstad E: Development of new glucocorticosteroids with a very high ratio between topical and systemic activities. Eur J Resp Dis Suppl 122, 63, 62-73, 1982.

Brattsand R, Källström L, Wieslander E, Andersson P, Dahlbäck M, Dahl R: A model for particle-induced inflammation and edema formation in the rat lung and the anti-inflammatory action of the glucocorticosteroid (GCS) budesonide in this model. European Society of Pneumology, Edinburgh Sept. 11th-16th, 49, 1983.

Brown HM: The introduction and early development of inhaled steroid treatment. In "Topical steroid treatment for asthma and rhinitis". Eds Mygind N, Clark THJ, Baillière Tindall, London 66-76, 1980.

Brown HM, Storey G, George WHS: Beclomethasone dipropionate: A new steroid aerosol for the treatment of allergic asthma. Br Med J 1, 585-590, 1972.

Burge PS, Efthimiou J, Turner-Warwick M, Nelmes PTJ: Double-blind trials of inhaled beclomethasone dipropionate and flucortin butyl ester in allergen-induced immediate and late asthmatic reactions. Clinical Allergy 12, 523-531, 1982.

Carrier HM, Giles A, Koelsche GA, Prickman LE, Maytum CK, Lake CF, Williams HL: The effect of cortisone on bronchial asthma and hay fever occurring in subjects sensitive to ragweed pollen. J Allergy 21, 282-287, 1950.

Chan L, O'Malley BW: Steroid hormone action: Recent advances. Ann Int Med 89, 694-701, 1978.

Claman HM: How corticosteroids work. J Allergy Clin Immunol 55, 145-151, 1975.

Clark THJ: Effect of beclomethasone dipropionate delivered by aerosol in patients with asthma. Lancet 1, 1361-1364, 1972.

Clark THJ, Costello JF, Soutar CA: The effects of beclomethasone dipropionate aerosol given in high doses to patients with asthma. Postgraduate Medical Journal 51 (Suppl 4), 72-75, 1975.

Cochrane GM: Systemic steroids in asthma. In "Steroids in asthma. A reappraisal in the light of inhalation therapy". Ed Clark THJ, 103-120, 1983.

Dahl R, Johansson SÅ: Effect on lung function of budesonide by inhalation, terbutaline s.c. and placebo given simultaneously or as single treatments. Eur J Resp Dis 63, Suppl 122, 132-137, 1982^a.

Dahl R, Johansson SÅ: Clinical effect of b.i.d. and q.i.d. administration of inhaled budesonide. A double-blind controlled study. Eur J Resp Dis 63, Suppl 122, 268-269, 1982^b.

Dahlberg E, Thalén A, Brattsand R, Gustafsson JÅ, Johansson U, Roempke K, Saartok T: Correlation between chemical structure, receptor binding and biological activity of some novel, highly active 16 α , 17 α -acetal substituted glucocorticoids. Molecular Pharmacol. Accepted for publication 1984.

Davies D: Pharmacokinetics of inhaled substances. Scand J Resp Dis Suppl 103, 44-49, 1978.

Dugue P, Orehek J, Arnaud A, Charpin J: Effect d'une injection d'hydrocortisone sur l'obstruction bronchique de l'asthme. Bull Europ Physiopathol Respir 13, 619-627, 1977.

Ellul-Micallef R, Fenech FF: Intravenous prednisolone in chronic bronchial asthma. *Thorax* 30, 312-315, 1975.

El-Shaboury AH, Williams DA: Betamethasone valerate aerosol in asthmatic patients receiving long-term oral steroid therapy: a double-blind controlled trial and follow up of patients for 20 months. *Postgraduate Medical Journal Suppl* (Sept) 15-17, 1974.

Foulds WS, Greaves DP, Herxheimer H, Kingdom LG: Hydrocortisone in the treatment of allergic conjunctivitis, allergic rhinitis and bronchial asthma. *Lancet* Jan 29, 234-235, 1955.

Franklin W, Lowell FC, Michelson AL, Schiller IW: Aerosolized steroids in bronchial asthma. *J Allergy* 29, 214-221, 1958.

Gaddie J, Petrie GR, Reid IW, Sinclair DJM, Skinner C, Palmer KNV: Aerosol beclomethasone dipropionate: a dose-response study in chronic bronchial asthma. *Lancet* Aug 11, 280- 281, 1973.

Gelfand ML: Administration of cortisone by the aerosol method in the treatment of bronchial asthma. *N Engl J Med* 245, 293-294, 1951.

Gibson GJ: Pathophysiology and clinical correlates of asthma. In "Steroids in asthma. A reappraisal in the light of inhalation therapy". Ed Clark THJ 10-31, 1983.

Harris DM: Clinical pharmacology of beclomethasone dipropionate. In "Topical steroid treatment for asthma and rhinitis". Eds Mygind N, Clark THJ, Baillière Tindall, London, 34-47, 1980.

Hartman FA: A further study of the hormone of the adrenal cortex. *Am J Physiol* 95, 670-680, 1930.

Hench PS, Kendall EC, Slocumb CH, Polley HF: The effect of a hormone of the adrenal cortex (17-hydroxy-11-dehydrocorticosterone: compound E) and of pituitary adrenocorticotrophic hormone on rheumatoid arthritis. *Staff meetings of the Mayo Clinic* 24, 181-197, 1949.

Henriksen JM, Dahl R, Johansson SÅ: Exercise induced bronchoconstriction: Effect of inhaled budesonide and terbutaline. XI Int Congress of Allergology and Clin Immunol, London 250, 1982.

Hirata F, Axelrod J: Phospholipid methylation and biological signal transmission. Science 209, 1082-1090, 1980.

Hochhaus G, Möllmann H, Rodhewald P: Affinity of glucocorticoids to their receptors in adult human lung. Am Pharm Assoc, Miami Nov, 1983.

Johansson SÅ, Andersson KE, Brattsand R, Hedner P, Gruvstad E: Topical and systemic glucocorticoid potencies of budesonide, beclomethasone dipropionate and prednisolone in man. Eur J Resp Dis Suppl 122, 63, 74-82, 1982.

Kiviloog J, Tivenius L, Glennow C: The effect of budesonide on bronchial provocation after varying lengths of pre-treatment. Eur J Resp Dis 63, 126, 1982.

Klaustermeyer WB, Hale FC: The physiologic effect of an intravenous glucocorticoid in bronchial asthma. Annals of Allergy 37, 80-86, 1976.

Kristensen JK, Wadkov S, Henriksen O: Effect of topical corticosteroids on blood flow in human cutaneous tissue. European Society for Dermatological Research, Abstracts 1971-1980, 274, 1977.

Lal S, Harris DM, Bhalla KK, Singhal SN, Butler AG: Comparison of beclomethasone dipropionate aerosol and prednisolone in reversible airway obstruction. Br Med J 3, 314-317, 1972.

Löfdahl CG, Mellstrand T, Svedmyr N: Comparison of systemic glucocorticoid potency of budesonide (B) and beclomethasone dipropionate (BDP) in man. II World Conference on Clinical Pharmacology and Therapeutics, Washington DC, July 31-Aug 5, 60, 1983.

Lowell FC, Ohman JL, Williams M: Double-blind trial of inhaled flunisolide in bronchial asthma. *J Allergy Clin Immunol* 57, 257, 1976.

Lowell FC, Schiller IW, Leard SE, Franklin W: Prolonged treatment of bronchial asthma with cortisone. *J Allergy* 24, 112-119, 1953.

Luksza AR: Acute severe asthma treated without steroids. *Br J Dis Chest* 76, 15-19, 1982.

Lundgren R: Scanning electron microscope studies of bronchial mucosa before and during treatment with beclomethasone dipropionate inhalations. *Scand J Resp Dis Suppl* 101, 179-188, 1977.

Martin GL, Atkins PC, Dunsky EH, Zweiman B: Effects of theophyllin, terbutaline and prednisone on antigen-induced bronchospasm and mediator release. *J Allergy Clin Immunol* 66, 204-212, 1980.

McFadden FR, Kiser R, DeGroot WJ, Homes B, Kiker R, Viser G: A controlled study of the effects of a single dose of hydrocortisone on the resolution of acute attack of asthma. *Am J Med* 60, 52-57, 1976.

Medical Research Council: Controlled trial of effects of cortisone acetate in status asthmaticus. *Lancet* Oct 20, 803-806, 1956.

Mishler JM: The effects of corticosteroids on mobilization and function of neutrophils. *Exp Hematol* 5, 15-32, 1977.

Munch EP, Taudorf E, Weeke B: Dose frequency in the treatment of asthmatics with inhaled topical steroid. *Eur J Resp Dis* 63, Suppl 122, 143-153, 1982.

Mygind N, Hansen I: Beclomethasone dipropionate aerosol effect on the adrenals in normal persons. *Acta Allergol* 28, 211-218, 1973.

Pepys J: Effects of inhaled beclomethasone dipropionate on bronchial provocation test reactions. Postgraduate Medical Journal 51 (Suppl 4), 42-48, 1975.

Pipkorn U, Andersson P: Budesonide and nasal mucosal histamine content and anti-IgE induced histamine release. Allergy 37, 591-595, 1982.

Reichstein T, Schoppee CW: The hormones of the adrenal cortex. Vitamin Horm I, 346-413, 1943.

Rosenhall L, Lundqvist G, Ädelroth E, Glennow C: Comparison between inhaled and oral corticosteroids in patients with chronic asthma. Eur J Resp Dis 63, Suppl 122, 154-162, 1982.

Ryrfeldt Å, Andersson P, Edsbäcker S, Tönnesson M, Davies D, Pauwels P: Pharmacokinetics and metabolism of budesonide, a selective glucocorticoid. Eur J Resp Dis Suppl 122, 63, 86-95, 1982.

Sarett LH: Partial synthesis of pregnene-4-triol 17(β), 20(β), 21-dione-3, 11 and pregnene 4-diol 17(β), 21, trione, 3, 11, 20, monoacetate. J Biol Chem 162, 601-631, 1946.

Savidge RS, Brochbank W: Long-term control of severe bronchial asthma with oral cortisone. Lancet ii, 889-893, 1954.

Smith MJ, Hodson ME: Effect of long term inhaled high-dose beclomethasone dipropionate on adrenal function. Thorax 38, 676-681, 1983.

Sugio K, Tsurufuji S: Mechanism of anti-inflammatory action of glucocorticoids: Re-evaluation of vascular constriction hypothesis. Br J Pharmacol 73, 605-608, 1981.

Swartz SL, Dluhy RG: Corticosteroids: clinical pharmacology and therapeutic use. Drugs 16: 238-255, 1978.

Svedmyr N: Effects of glucocorticoids on the airways. Eur J Resp Dis 63, Suppl 122, 48-53, 1982.

Svensjö E: Microvascular aspects of edema formation and its inhibition by beta-2-stimulants and some anti-inflammatory drugs. The second Australian and New Zealand symposium on the micro-circulation. Aug 25-27 1983.

Swingle WW, Pfiffner JJ: Experiments with an active extract of the suprarenal cortex. Anat Rec 44, 225-226, 1930.

Thalén A, Brattsand R: Synthesis and anti-inflammatory properties of budesonide, a new non-halogenated glucocorticoid with high local activity. Arzneimittel/Forsch/Drug Res 29, 1687-1690, 1979.

Thiringer G, Eriksson N, Malmberg R, Svedmyr N, Zettergren L: Bronchoscopic biopsies of bronchial mucosa before and after beclomethasone dipropionate therapy. Scandinavian J Resp Dis, Suppl 101, 173-176, 1977.

Toogood JH, Lefcoe NM: Dexamethasone aerosol for the treatment of steroid dependent chronic bronchial asthmatic patients. J Allergy 36, 321-322, 1965.

Toogood JH, Lefcoe NM, Haines DSM, Jennings B, Errington N, Baksh L, Chuang L: A graded dose assessment of the efficacy of beclomethasone dipropionate aerosol for severe chronic asthma. J Allergy 59, 298-308, 1977.

Toogood JH, Jennings B, Baskerville J, Lefcoe NM, Johansson SÅ: Comparison of alternate morning prednisone vs inhaled steroid for asthma. Annals Royal Coll Phys Surg (Can) 16, 4, 308, 1983.

Walton J, Watson BS, Ney RL: Alternate-day versus shorter interval steroid administration. Arch Int Med 126, 601-607, 1970.

Vaz R, Senior B, Morris M, Binkiewicz A: Adrenal effects of beclomethasone inhalation therapy in asthmatic children. *J of Pediatrics* 100, 660-662, 1982.

Willey RF, Godden DJ, Carmichael J, Preston P, Frame MH, Crompton GK: Comparison of twice daily inhalation of a new corticosteroid, budesonide, with beclomethasone dipropionate four times daily in the treatment of chronic asthma. *Br J Dis Chest* 76, 61-68, 1982.

Wyatt R, Waschek J, Weinberger M, Sherman B: Effect of inhaled beclomethasone dipropionate and alternate day prednisone on pituitary-adrenal function in children with chronic asthma. *N Engl J Med* 299, 25, 1387-1392, 1978.

Yodoi J, Hirashima M, Ishazaka K: Lymphocytes bearing FC-receptors for IgE. VI. Suppressive effect of glucocorticoids on the expression of FC receptors and glycosylation of IgE-binding factors. *J Immunol* 127, 471-476, 1981.

I

Topical and Systemic Glucocorticoid Potencies of Budesonide and Beclomethasone Dipropionate in Man

S.-Å. Johansson¹, K.-E. Andersson², R. Brattsand³, E. Gruvstad¹, and P. Hedner⁴

¹Medical Department, AB Draco, ²Department of Clinical Pharmacology, University of Lund,

³R & D Department, AB Draco, and ⁴Medical Department, University of Lund, Lund, Sweden

Summary. Topical anti-inflammatory (cutaneous "vasoconstriction") and systemic glucocorticoid (depression of plasma cortisol and changes in differential WBC count) potencies of the two glucocorticoids budesonide and beclomethasone dipropionate (BDP) were compared in human volunteers. After topical application, budesonide was 2–3 times more potent than BDP in inducing "vasoconstriction". After oral administration, on the other hand, budesonide was 2–4 times less potent than BDP in depressing plasma cortisol and changing the total or differential WBC. After inhalation, too, significant differences in favour of budesonide were noted, but the divergence between the drugs was less pronounced. The improved relationship between the topical and systemic glucocorticoid effects of budesonide makes it a promising alternative for aerosol treatment in asthma.

Key words: beclomethasone dipropionate, budesonide, glucocorticoids, aerosol; plasma cortisol, differential WBC, topical effect, topical administration

The introduction of beclomethasone dipropionate (BDP) aerosol brought about new possibilities for the effective local steroid treatment of asthma, combined with a reduced risk of systemic glucocorticoid reactions (Brown et al. 1972; Clark 1972; Toogood et al. 1977). BDP has a high intrinsic glucocorticoid activity, but is rapidly hydrolyzed by esterases to corticoids of lower activity (Martin et al. 1974). This is probably the reason why BDP has a high topical glucocorticoid activity in the lung but comparatively little systemic activity. The esterases are present in the lung, which results in partial biotransformation during the absorption of BDP (Hartiala et al. 1979), and theoretically this should diminish its local glucocorticoid potency. This might partly explain the find-

ings that a number of patients with asthma have to continue oral corticosteroids besides the BDP-aerosol (Brown and Storey 1975; Toogood et al. 1978). A further disadvantage of the present glucocorticoid aerosol treatment with BDP is that systemic actions have been noted especially when the dose is increased (Mygind and Hansen 1973; Toogood et al. 1977; Wyatt et al. 1978).

Budesonide is a potent non-halogenated 16,17-acetal corticoid (Thalén and Brattsand 1979; Brattsand et al. 1981), which is effectively biotransformed in the liver via oxidative and reductive biotransformation, but not in the lung or skin (Andersson et al. 1981; Ryrfeldt et al. 1981). The aim of the present investigation was to assess the topical anti-inflammatory and systemic glucocorticoid potencies of budesonide in man and to compare them with those of BDP, as the drugs are biotransformed via different routes. A glucocorticoid which was not inactivated by local biotransformation in the lung might be of great clinical interest, as this should lead to more effective aerosol therapy in asthma.

Materials

Topical Administration

12 healthy volunteers participated in the first study, 5 females and 7 males; mean age 32 years (range 24–46 years). In the second study there were 10 healthy volunteers, 5 females and 5 males; mean age 32 years (range 24–46 years).

Oral Administration

Eight healthy volunteers participated in the study, one female and seven males; mean age 28 years (range 22–38 years), and mean weight 71 kg (range 50–82 kg).

Aerosol Administration

Twelve subjects were included in the aerosol administration study, two females and ten males; mean age 28 years (range 22–38 years), and mean weight 70 kg (range 50–82 kg). 7 of the subjects in this study had also participated in the oral administration study.

None of the volunteers received any other drug and none of them had any sign or symptom of disease; their total and differential WBC-counts and plasma cortisols were all within the normal values for the laboratory.

Methods

I. Topical Anti-Inflammatory Potency

The blanching tests were performed according to the method of Place (1970). Test sites 7×7 mm were outlined with silicone grease on the flexor surface of the forearms of the volunteers. 10 μ l of each test solution was administered, and when the diluent had evaporated the arm was covered with plastic film for 18 h. The dressing was then removed, the arm washed with ethanol and the degree of blanching (vasoconstriction) estimated 1, 2, 3, 6, 12 and 24 h after removing the plastic film. The blanching was graded according to a four-point scale where 0 denoted normal skin, 1 faint blanching, 2 manifest blanching and 3 intense blanching. Twelve sites for each concentration were used in a test in which six glucocorticoids were compared, and 30 test sites were used in a second study comparing BDP and budesonide. The EC_{50} value is defined here as the concentration at which 50% of the test sites displayed at least a Grade 2 reaction (manifest blanching) at two of the three first readings after removal of the plastic film. Time-effect curves were constructed for all substances, and doses and relative potency values based on the area under the curves (AUC) were calculated from parallel regression lines using Fieller's theorem (Finney 1952).

Drugs and Doses

Serial dilutions of the following drugs contained in 95% ethanol were made in the following concentrations:

Dexamethasone isonicotinate: 1×10^{-4} , 3×10^{-5} , 1×10^{-5} , 3×10^{-6} , and 1×10^{-6} g/ml

Triamcinolone acetonide 3×10^{-5} , 1×10^{-5} , 3×10^{-6} , 1×10^{-6} , and 3×10^{-7} g/ml

BDP, betamethasone-17-valerate, budesonide and fluocinolone acetonide: 1×10^{-5} , 3×10^{-6} , 1×10^{-6} , 3×10^{-7} , and 1×10^{-7} g/ml

II. Systemic Glucocorticoid Potency

For the systemic effect studies the method described by Buniva et al. (1979) was used, with a number of modifications. The investigation of each drug, dose and administration form was performed on two consecutive days, Day 1 always being the placebo day. The drugs and placebos were given in the evening at 10 p.m. on the day before the investigation. On trial days, the subject came to the clinic at 8 a.m., 10 a.m. and at noon. A venous blood sample was taken on each occasion and total and differential white cell counts were made with a Coulter Counter and by counting 500 cells. Plasma was prepared and stored at -20°C until analysed for cortisol by radioimmunoassay (New England Nuclear).

All tests were performed as double-blind crossover studies, and the drugs were given in randomized order according to a table of random numbers (Armitage 1974).

On each trial day, the subjects were asked whether they had experienced any side-effects.

The oral study was performed first and was completed when the aerosol study began. One week elapsed between two adjacent runs in each subject. Before the aerosol part of the study started, the subjects were trained in handling a pressurized aerosol.

Before agreeing to participate in the trial, all subjects were thoroughly informed about the study and about all possible risks and inconveniences that might be expected during the trial. The design of the studies was reviewed and approved by the Ethical Committee of the University of Lund, and by the Drug Department of the National Social Welfare Board of Sweden.

The Drugs and Doses used were:

1. *Oral administration study.* BDP and budesonide 2, 4, and 8 mg. The drugs were given in micronized form in gelatine capsules, with lactose as a vehicle and as sole content in the placebo capsules. The capsules were filled at AB Draco, Lund, Sweden.

2. *Aerosol administration study.* BDP 200 (4 puffs of 50 μ g), 800 (16 puffs of 50 μ g), and 3250 μ g (13 puffs of 250 μ g). Budesonide 200 (4 puffs of 50 μ g), 800 (4 puffs of 200 μ g) and 3200 (16 puffs of 200 μ g). The drugs were inhaled from a pressurized aerosol. The BDP aerosols (batch no. 7NR778 and NPTH/78) were manufactured by Allen & Hanburys, Ware,

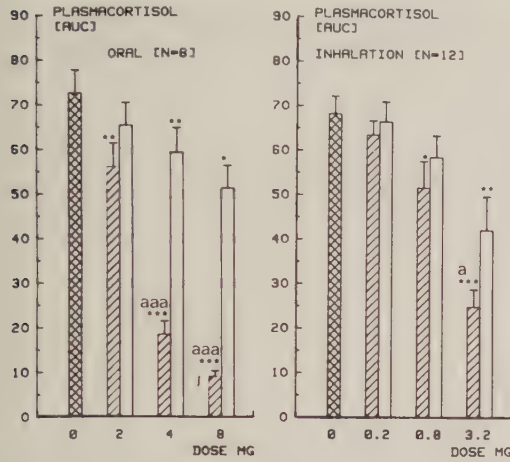


Fig. 1. Area under curve of plasma cortisol

PLACEBO
 BDP
 BUD

* $p < 0.05$
 ** $p < 0.01$
 *** $p < 0.001$

a $p < 0.05$
 aa $p < 0.01$

diff. vs. placebo

diff. between BDP and BUD

Table 1. Vasoconstriction: results of Test I

Corticosteroid	EC ₅₀ [µg/ml]	95% confidence interval	Rel. potency (area under curves)
Dexamethasone isonicotinate	19.1	53.8–11.0	0.02
Triamcinolone acetonide	6.1	10.8– 3.6	0.2
Beclomethasone dipropionate	3.1	5.3– 1.9	0.3
Fluocinolone acetonide	3.1	6.4– 1.8	0.5
Betamethasone valerate	2.1	4.2– 1.2	0.3
Budesonide	1.0	1.5– 0.6	1

Table 2. Vasoconstriction: results of Test II

Corticosteroid	EC ₅₀ [µg/ml]	95% confidence interval	Rel. potency (area under curves)
Beclomethasone dipropionate	1.2	1.8–0.9	0.5
Budesonide	0.5	0.6–0.4	1

Hertfordshire, UK, and the budesonide aerosols (batch no. DFB-4-B) by AB Draco, Lund, Sweden.

Statistical Evaluation

In the "vasoconstriction" test, probit transformation was used to linearize the data and calculate the EC₅₀ values.

When comparing the plasma cortisol values, Student's *t*-test was used, and relative potency values based on area under the curves (AUC) were calculated from parallel regression lines. For evaluation of other systemic effects, Wilcoxon's rank test was used. For all variables, the level of significance was calculated from the paired differences.

Results

Topical Anti-Inflammatory Potency

In the "vasoconstriction" test, budesonide was more potent than the other drugs tested. The EC₅₀ values and 95% confidence intervals, and relative potencies of the drugs under investigation are listed in Table 1 and 2. Repetition of the assays of BDP and budesonide (the second study) showed a slight difference in absolute potency, but there was consistency of their relative potency. The area under curve (AUC) was also investigated; it showed the order between the

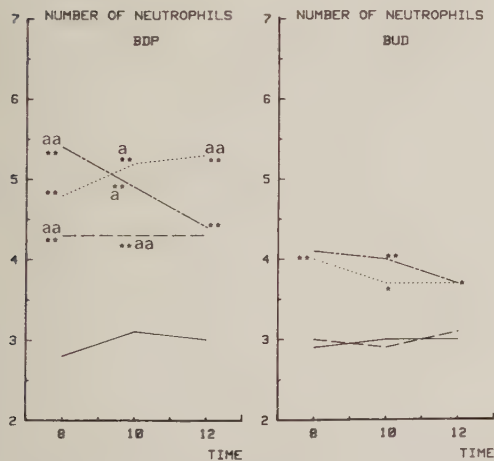


Fig. 2. Median number of neutrophils $\times 10^9/l$ after oral administration ($n = 8$)

* $p < 0.05$
 ** $p < 0.01$

a $p < 0.05$
 aa $p < 0.01$

diff. vs. placebo

diff. between BDP and BUD

— Placebo
 --- 2 mg
 4 mg
 -.-.- 8 mg

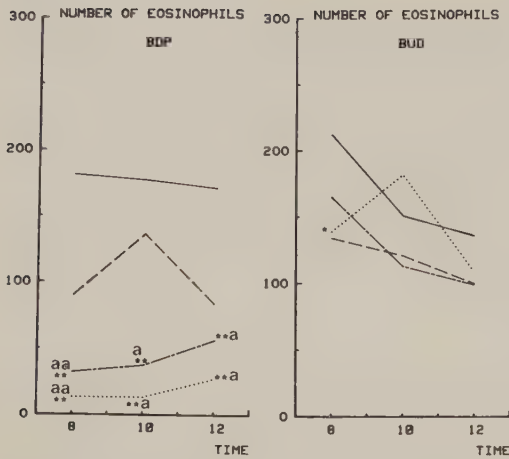


Fig. 3. Median number of eosinophils $\times 10^6/l$ after oral administration ($n = 8$)

* $p < 0.05$ } diff. vs. placebo
 ** $p < 0.01$ }
 a $p < 0.05$ } diff. between
 aa $p < 0.01$ } BDP and BUD

— Placebo
 --- 2 mg
 - - - 4 mg
 8 mg

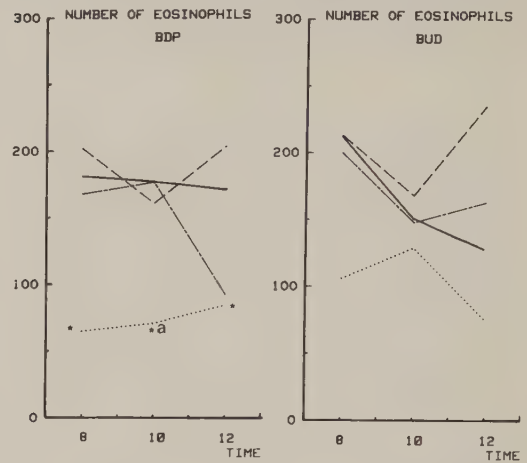


Fig. 4. Median number of eosinophils $\times 10^6/l$ after inhalation ($n = 12$)

* $p < 0.05$ } diff. vs. placebo
 a $p < 0.05$ } diff. between
 BDP and BLID

— Placebo
 --- 0.2 mg
 - - - 0.8 mg
 3.2 mg

Table 3. Number of lymphocytes ($\times 10^9/l$) 10 (8 a.m.), 12 (10 a.m.) and 14 (noon) h after oral dosing with BDP, budesonide or placebo; median, minimum and maximum ($n = 8$)

Time	BDP									Budesonide								
	8 a.m.			10 a.m.			noon			8 a.m.			10 a.m.			noon		
Dose [mg]	Med	Min	Max	Med	Min	Max	Med	Min	Max	Med	Min	Max	Med	Min	Max	Med	Min	Max
Placebo (3 $\times$ 8 observations)	2.4	1.5	4.0	2.1	1.3	3.6	1.9	1.4	2.9	2.4	1.5	3.1	2.0	1.4	2.8	2.0	1.3	3.4
2	2.0	1.8	3.1	1.8	1.3	2.7	2.0	1.5	8.0	2.0	1.9	3.6	2.0	1.5	2.3	2.1	1.6	2.9
4	1.9	1.2	2.9	1.9	1.2	2.7	1.8	1.4	2.7	2.7	2.0	4.0	1.8	1.5	2.5	2.0	1.7	2.7
8	1.4	1.0	2.8	1.2	0.9	2.9	1.5	1.2	2.3	2.2	1.5	2.6	1.8	1.4	3.0	1.8	1.5	2.8

Diff. vs. placebo * $p < 0.05$
 ** $p < 0.01$

Diff. between BDP and Budesonide a $p < 0.05$

drugs to be the same, except that flucinolone acetonide was slightly more potent than betamethasone valerate.

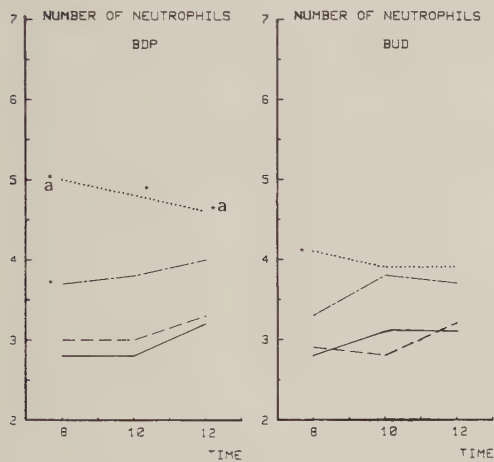
Systemic Glucocorticoid Potency

1. *Oral Administration.* There was a statistically significant decrease in plasma cortisol at 8 a.m. after budesonide 2 and 8 mg, and at noon after budesonide 4

and 8 mg, but none of the dose levels significantly depressed plasma cortisol at all three observation times. Plasma cortisol was significantly reduced at all observation times after all doses of BDP, except at 10 a.m. and at noon after the 2 mg dose. When the drugs were compared, significantly lower plasma cortisol values were noted after BDP than after corresponding doses of budesonide except at 10 a.m. and at noon after the 2 mg dose. Regarding the area

Table 4. Number of lymphocytes (median, minimum, maximum; $\times 10^9/l$) 10 (8 a.m.), 12 (10 a.m.) and 14 (noon) h after inhalation of BDP, budesonide or placebo ($n = 12$)

Time Dose [mg]	BDP									Budesonide								
	8 a.m.			10 a.m.			noon			8 a.m.			10 a.m.			noon		
	Med	Min	Max	Med	Min	Max	Med	Min	Max	Med	Min	Max	Med	Min	Max	Med	Min	Max
Placebo (3 $\times$ 8 observations)	2.5	1.3	4.9	2.2	0.8	3.3	2.1	1.1	3.7	2.5	1.2	5.6	2.1	1.3	3.5	2.2	1.0	3.6
0.2	2.5	1.6	3.6	1.9	1.0	2.8	2.0	1.2	2.9	2.6	1.9	3.7	2.2	1.5	2.9	2.1	1.4	4.1
0.8	2.3	1.2	3.5	1.9	1.2	2.7	2.1	1.0	3.8	2.5	1.3	3.3	2.0	1.0	2.8	2.2	1.1	2.9
	*			*						a								
3.2	1.8	1.4	3.2	1.8	1.4	2.9	2.1	1.6	2.7	2.3	1.6	3.1	2.3	1.4	2.6	2.3	1.7	3.1
Diff. vs. placebo	* $p < 0.05$									Diff. between BDP and Budesonide a $p < 0.05$								

**Fig. 5.** Median number of neutrophils $\times 10^9/l$ after inhalation ($n = 12$)

* $p < 0.05$ diff. vs. placebo
 a $p < 0.05$ } diff. between BDP and BLID

under the curves (AUC), all doses of BDP depressed the cortisol values, but only the 4 and the 8 mg doses of budesonide caused significantly lower levels than the placebo (Fig. 1), and at these dose levels there were also significant differences between the drugs. The slope of the regression line for plasma cortisol was found to be nonsignificant for budesonide and highly significant for BDP, with a significant difference between them ($p < 0.01$).

The changes in the numbers of lymphocytes, neutrophils and eosinophils were also significantly greater

after BDP than after budesonide (Figs. 2 and 3 and Table 3). Regarding an effect on the monocytes, the two high BDP doses caused a statistically significant fall at 8 a.m., whereas budesonide did not decrease the count at any dose level.

2. Aerosol Administration. There was a statistically significant decrease in plasma cortisol at noon after BDP 0.2 mg, at 8 and 10 a.m. after BDP 0.8 mg, and at all observation times after BDP 3.2 mg, whereas only the highest aerosol dose of budesonide had any statistically significant influence on the plasma cortisol level. There were significant differences between the drugs at noon after 0.2 and 3.2 mg. When the areas under the curves (AUCs) for plasma cortisol-time were investigated, they were found to be significantly decreased after BDP 0.8 and 3.2 mg, but only after 3.2 mg budesonide (Fig. 1). At the highest dose level there was a significant difference between the drugs ($p < 0.05$) in favour of budesonide. The relative potency for inducing a decrease in plasma cortisol was found to be 0.44 for budesonide when BDP was given the value 1; the difference was significant ($p < 0.05$).

Lymphocytes and eosinophils were more depressed after BDP than after budesonide (Fig. 4; Table 4). Neutrophils increased more after BDP than after budesonide (Fig. 5). There was no significant effect on monocytes of any of the drugs.

Adverse Effects

There was no difference between the active drugs and placebo in the frequency of side-effects. In the oral administration study, two subjects on BDP and one on budesonide complained of stomachache while on the highest dose. No adverse effects were

reported in the inhalation study except local irritation of short duration, probably due to the large number of inhalations.

Discussion

A topical anti-inflammatory effect is thought to be the main mechanism of action of corticosteroids in the treatment of asthma (Claman 1975). There are no relevant models for determination of the topical anti-inflammatory potency in the lung. Therefore, we decided to use the topical anti-inflammatory potency, expressed as the ability to induce "vasoconstriction" in the forearm in human volunteers. This has also been suggested by Harris (1980) as the first step in assessing the properties of a corticosteroid for inhalation therapy in man. In order to avoid differences in percutaneous adsorption, the test was done with the occlusion technique, as this greatly enhances absorption. With such high absorption, and with the low extent of local biotransformation of at least 16,17-acetalcorticosteroids in the skin (Andersson et al. 1981) the "vasoconstriction" test mainly reflects intrinsic glucocorticoid potency. There is a good correlation between the ability to induce "vasoconstriction" in normal human skin and the ability to produce improvement in inflammatory skin disorders (McKenzie and Stoughton 1962).

Of the six corticoids tested, representing both 16,17-acetal and 17- or 17,21-esterified corticoids, budesonide had the highest "intrinsic" glucocorticoid potency. It was 2–3 times more potent than BDP. This may be in accordance with its topical anti-asthmatic potency as an aerosol, as budesonide in a daily dose of 200 µg had a similar anti-asthmatic effect to that of 400 µg/day of BDP-aerosol (Björkander et al. 1982).

The investigation of systemic glucocorticoid effects showed that both drugs produced the same maximal effect, but also that BDP was more potent than budesonide. After oral administration BDP 2–4 mg produced the same or even more profound systemic actions than budesonide 8 mg. After aerosol administration, the threshold doses of both drugs for significant systemic glucocorticoid actions varied between 0.8–3.2 mg, but still suggesting that BDP had about the twice the systemic potency of budesonide. In another study of systemic glucocorticoid activity, the glucocorticoid betamethasone 17,21 dipropionate was significantly more potent than budesonide on application to the skin of human volunteers (Scott et al. 1981).

Regarding the haematological parameters, a dose-response relationship was found for both drugs

and for most parameters, with BDP being most potent. The results in the vasoconstriction tests combined with those of the systemic studies show that it is possible to improve the relationship between topical and systemic glucocorticoid effects over that reached with BDP. A difference in pharmacokinetic behaviour is the probable explanation of the different topical/systemic-relationship of the two drugs. BDP is biotransformed to less active glucocorticoids (Martin et al. 1974) by esterases present in several tissues, including the lung (Hartiala et al. 1979), while budesonide is mainly and efficiently biotransformed by oxidative and reductive biotransformation in the liver (Andersson et al. 1981).

By comparing the threshold doses for systemic glucocorticoid activity after oral and aerosol administration, it is possible to assess how much the orally deposited and swallowed part of an aerosol dose contributes to its systemic activity. For budesonide significant systemic actions were noted after an aerosol dose of 3.2 mg, and these actions seem mainly to depend on the fraction absorbed in the lung, as the oral dose of 4 mg had much less systemic activity. The oral bioavailability in man of budesonide is about 11% (Ryrfeldt et al. 1981) and is probably also restricted for BDP (Martin et al. 1974; Harris 1980), although no exact figure has been reported. The low bioavailability of oral budesonide was verified in a clinical investigation by Ellul-Micallef et al. (1980), who, in the same group of patients, found that oral budesonide 1 mg had no anti-asthmatic activity, while the same dose given by inhalation had significant activity. Low oral bioavailability is of great importance for an aerosol corticoid, as the major portion of an aerosol dose is orally deposited and swallowed. The present results suggest that the profound systemic actions noted after BDP aerosol 3.2 mg might also depend to some extent on the proportion swallowed, as even 2 mg oral BDP significantly reduced the plasma cortisol level and affected differential WBC-count.

The improved relationship between the topical and systemic activities of budesonide as compared to those of BDP may be of clinical importance. The high topical potency of budesonide in combination with its metabolic stability in the lung raises the possibility of efficient treatment of patients with severe reversible chronic obstructive lung disease by inhalation alone with only negligible systemic effects (Rosenhall et al. 1982).

References

- Andersson P, Edsbäcker S, Ryrfeldt Å (1982) In vitro biotransformation of budesonide, triamcinoloneacetonide and hydrocorti-

- sone in liver and skin from man, rat and hairless mouse. *J Steroid Biochem* 16: 787–796
- Armitage P (1974) Statistical methods in clinical research. Blackwell, Oxford
- Björkander J, Formgren H, Johansson SÅ, Millquist E (1982) Methodological aspects on clinical trials with inhaled corticosteroids: Results of two comparisons between two steroid aerosols in patients with asthma. *Eur J Respir Dis Suppl* 122 (Vol 63) 108–117
- Brattsand R, Thalén A, Roempe K, Källström L, Gruvstad E (1982) Influence of 16 α , 17 α -acetal substitution and steroid nucleus fluorination on the topical to systemic activity of glucocorticoids. *J Steroid Biochemistry* 16: 779–786
- Brown MH, Storey G (1973) Beclomethasone dipropionate steroid aerosol in treatment of perennial allergic asthma in children. *Br Med J* 3: 161–164
- Brown MH, Storey G, George WHS (1972) Beclomethasone dipropionate: A new steroid aerosol for the treatment of allergic asthma. *Br Med J* 1: 585–590
- Brown MH, Storey G (1975) Treatment of allergy of the respiratory tract with beclomethasone dipropionate steroid aerosol. *Postgrad Med J* 51 (Suppl 4): 59–64
- Buniva G, Dubini A, Sassella D (1979) Human bioassay of corticotropin-suppressing eosinopenic and hyperglycaemic potencies of deflazacort and prednisone. *Curr Ther Res* 26: 69–81
- Claman HN (1975) How corticosteroids work. *J Allergy Clin Immunol* 55: 145–51
- Clark THJ (1972) The effect of beclomethasone tipropionate delivered by aerosol in patients with asthma. *Lancet* 1: 1361–1364
- Ellul-Micallef R, Hansson E, Johansson SÅ (1980) Budesonide A new corticosteroid in bronchial asthma. *Eur J Respir Dis* 61: 167–173
- Finney DJ (1952) Statistical method in biological assay. Hafner, New York
- Harris DM (1980) In: Topical steroid treatment for asthma and rhinitis. Clark THJ and Mygind N (eds) *Clinical Pharmacology of Beclomethasone dipropionate*. Baillere-Tindall, London, pp 34–47
- Hartiala J, Uotila P, Nienstedt W (1979) Absorption and metabolism of intratracheally instilled cortisol and beclomethasone dipropionate in the isolated perfused rat lungs. *Med Biol* 57: 294–297
- Martin LE, Tanner RJN, Clark THJ, Cochrane GM (1974) Absorption and metabolism of orally administered beclomethasone dipropionate. *Clin Pharmacol Ther* 15: 267–275
- McKenzie AW, Stoughton RB (1962) Method for comparing percutaneous absorption of steroids. *Arch Dermatol* 86: 608–610
- Mygind M, Hansen J (1973) Beclomethasone dipropionate aerosol effect on the adrenals in normal persons. *Acta Allergol* 28: 211–218
- Place VA, Velazquez JG, Burdick KH (1970) Precise evaluation of topically applied corticosteroid potency. *Arch Dermatol* 101: 531–537
- Rosenhall L, Lundquist G, Ådelroth E, Glennow C (1982) Comparison between inhaled and oral corticosteroids in patients with chronic asthma. *Eur J Respir Dis Suppl* 122 (Vol 63) 154–162
- Ryrfeldt Å, Andersson P, Edsbäcker S, Tönnesson M, Davies D, Pauwels R (1981) Pharmacokinetics of a selective glucocorticoid, budesonide. Proceedings of the Annual Meeting of European Academy of Allergology and Clinical Immunology, Clermont-Ferrand, France 704–708
- Ryrfeldt Å, Tönnesson M, Nilsson E, Wikby A (1979) Pharmacokinetics studies of a potent glucocorticoid (budesonide) in dogs by high performance liquid chromatography. *J Steroid Biochem* 10: 317–324
- Scott M, Malmsten LÅ, Thelin J (1981) Effect on plasma cortisol level and urinary cortisol excretion, in healthy volunteers, after application of three different topical steroid ointments under occlusion. *Acta Derm Venereol* 61: 543–546
- Thalén A, Brattsand R (1979) Synthesis and Anti-inflammatory properties of budesonide, a new non-halogenated glucocorticoid with high local activity. *Arzneim Forsch* 29 (II), 11: 1687–1690
- Toogood JH, Lefcoe NH, Haines DSM, Jennings B, Errington M, Baksh L, Chuang L (1977a) A graded doseassessment of the efficacy of beclomethasone dipropionate aerosol for severe chronic asthma. *J Allergy* 59: 298–308
- Toogood JH, Lefcoe NH, Haines DSM, Chuang L, Jennings B, Errington N, Baksh L, Cauchi M (1978) Minimum dose requirements of steroid-dependent asthmatic patients for aerosol beclomethasone and oral prednisone. *J Allergy* 61: 355–364
- Wyatt R, Waschek J, Weinberger M, Sherman B (1978) Effects of inhaled beclomethasone dipropionate and alternateday prednisone on pituitary-adrenal function in children with chronic asthma. *N Engl J Med* 299 (No.25): 1387–1392

Received: July 27, 1981

accepted in revised form: November 6, 1981

S.-Å. Johansson

Box 1707

S-22101Lund, Sweden

Importance of duration of treatment with inhaled budesonide on the immediate and late bronchial reaction

R DAHL¹ & S-Å JOHANSSON²

¹Department of Lung Medicine, Århus Kommunchospital, Århus, Denmark ²Medical Department, AB Draco*, Lund, Sweden

Abstract: The influence on the immediate and late bronchial allergic reaction after pretreatment with budesonide was investigated in 10 asthmatic patients with dual bronchial responses to bronchial provocation tests. Pretreatment was given in daily doses of 1 mg inhaled budesonide from a pressurized aerosol.

In the first study pretreatment was given for 12 h and one week and in the second study for one week and one month.

The late allergic reaction decreased markedly after 12 h pretreatment but additional effect was obtained after extended pretreatment. The immediate allergic reaction decreased less after pretreatment for 12 h and one week than did the late allergic reaction. Pretreatment for one month decreased also the immediate reaction substantially.

Key words: asthma – allergy – challenge test – immediate allergic reaction – late allergic reaction – budesonide.

Inhalation of allergens in patients with bronchial asthma may result in bronchial obstruction of immediate type, of late type, or of a combined dual reaction (5, 6, 15, 21). It is well established that pretreatment with glucocorticoids decreases or abolishes the late reaction (5, 6, 11, 21, 22, 23, 26) whereas the influence on the immediate reaction has been a matter of controversy (3, 5, 17, 21, 22, 23, 26). We therefore decided to investigate this question with the use of budesonide, a non-halogenated synthetic glucocorticoid (27) that has shown a more favourable ratio between topical anti-inflammatory and systemic activity than beclomethasone dipropionate (16). Inhaled budesonide is effective in asthma and rhinitis (2, 8, 28) and an anti-anaphylactic effect has been reported after nasal challenge tests (19, 24).

The studies reported below were undertaken to investigate the effect of inhaled budesonide on the immediate and late allergic reaction after bronchial provocation and of the influence of variation of the duration of pretreatment with budesonide on these reactions.

PATIENTS

Study 1

Ten patients, five males and five females, with a mean age of 29 years (range 17–42 years) were selected for the trial. They were all known to have a dual bronchial response to bronchial provocation. A pre-test confirmed the appropriate allergen dose and the dual response. One patient was sensitive to birch and nine to house dust mite.

*Subsidiary of AB Astra, Sweden.

Study 2

Ten patients, four males and six females, with a mean age of 31 years (range 18–43 years) took part in this trial. Eight of the patients had participated also in the first study. One patient was sensitive to birch; one, to cat; and eight, to house dust mite.

All the patients in the trials had had asthma for at least 5 years but had, at the time of the trial, normal or practically normal lung function. Their asthma was clinically mild and this was not attributable to drug treatment. They all had a positive clinical history, positive prick-test and RAST for the allergen used for the provocations. From earlier provocations they were known to have a dual bronchial response to bronchial provocation and the interval between provocation for the occurrence of a late reaction in a given patient was predictable (unpublished data). All drug treatment, except pressurized beta₂-receptor agonist aerosols, which were allowed for occasional use but not later than eight hours before a test, was stopped at least one week before the trials.

METHOD

Inhalation challenge was performed with a Hudson nebulizer with a flow of 5 l/min. The allergens used originated from the Allergologisk Laboratorium, Copenhagen, Denmark. In a pretest the allergen dose that reduced PEF by 15–40 % within 30 min after challenge was established. This dose was used in the following challenges. After the immediate reaction lung function was allowed to recover spontaneously, which occurred within two hours. A late reaction was defined as a subsequent fall in PEF of ≥ 25 % of the initial value.

Study 1

One week after the pretest the patients returned for a second challenge. They inhaled 1 mg budesonide (five inhalations à 200 µg) from a freon propelled metered aerosol on the previous evening at 8 o'clock and 1 mg in the morning, four hours before the challenge test. The patients then continued to inhale budesonide 1 mg a day for seven days (400 µg in the morning and 600 µg in the evening) and then returned for a third challenge, when they again inhaled 1 mg four hours before the test.

Study 2

After the pre-test, the patients inhaled 1 mg budesonide a day (400 µg in the morning and 600 µg in the evening) for four weeks and returned after respectively one and four weeks for new challenge tests. As in study 1 budesonide 1 mg was inhaled four hours before the challenge.

In both studies lung function was assessed from PEF-measurements 15 min before challenge and 5, 10, 15, 20, 30, 45 and 60 minutes after challenge and then every 30 min for at least seven hours. Three measurements were made each time. The highest was recorded and used for the statistical calculations. Both trials were open. All challenges in a given patient were performed at the same time of the day.

All patients were informed about the trials in advance and all volunteered to participate.

Statistical method

The statistical analyses were based on the paired differences and Student's *t*-test.

RESULTS

Study 1

Mean PEF-values in the first study are shown in Figure 1. All values after the provocation of the control challenge were significantly lower than the pre-test values ($p < 0.05$), thus, lung function did not recover completely during the time of observation. No values are given after the fourth hour because some patients then required treatment of severe bronchospasm. After budesonide 1 + 1 mg the values decreased significantly from five to 60 min (immediate reaction) and after six to eight hours (late reaction) compared to the pre-test value ($p < 0.05$). When the patients had used budesonide for seven days only the values recorded 5–45 min after challenge were lower than the pre-test values ($p < 0.05$). The mean maximum responses during the immediate and late reaction are shown in Table 1. There was a significant fall in PEF for the immediate and late reactions after all challenges with the exception of the late reaction after one week's treatment with budesonide, and the fall after pre-treatment with budesonide was significantly lower than in the control challenge. After one week's treatment the fall in PEF was smaller than after the short pre-treatment. The effect of the treatment on the immediate reaction was also assessed from the mean areas under the curves (AUC) from 0–60 min (Table 2). After one week's treatment the reaction tended to be decreased, but the difference was not significant.

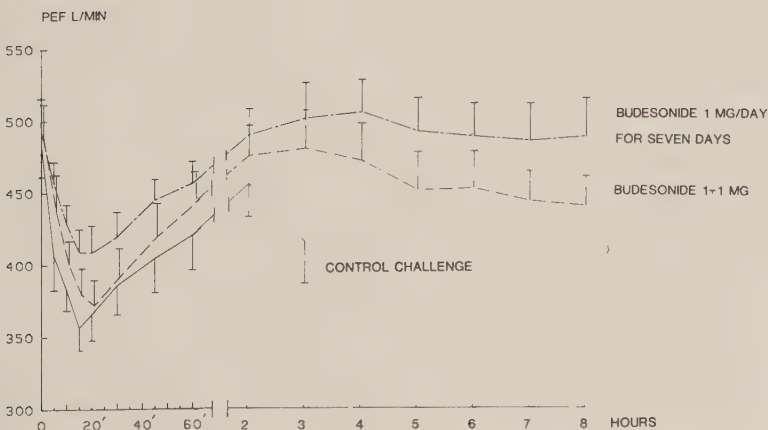


Figure 1. Mean PEF $\pm$ SEM (l/min) from 0 to 8 hours after control challenge and after pretreatment with budesonide for 12 h and one week ($n = 10$).

Table 1.

PEF-values before and maximum response after bronchial challenge with allergen ($M \pm SEM$, $n=10$).

Treatment	Prevalue PEF l/min	Immediate reaction		Late reaction	
		PEF l/min	% fall in PEF	PEF l/min	% fall in PEF
Control	485 $\pm$ 23	*** 345 $\pm$ 16	*** 28.5 $\pm$ 2.5	*** 302 $\pm$ 22	*** 36.6 $\pm$ 4.9
Budesonide 1 + 1 mg	489 $\pm$ 23	***a 370 $\pm$ 18	*** 23.8 $\pm$ 3.4	***aaa 408 $\pm$ 27	***aaa 16.3 $\pm$ 4.4
Budesonide for one week	493 $\pm$ 23	**a 404 $\pm$ 17	**ab 16.8 $\pm$ 4.4	aaa,bb 462 $\pm$ 22	aaa,bb 5.9 $\pm$ 3.1

** $p < 0.01$ Diff v pre-value

*** $p < 0.001$

a $p < 0.05$ Diff v control

aaa $p < 0.001$

b $p < 0.05$ Diff v Bud 1 + 1 mg

bb $p < 0.01$

Study 2

The mean PEF-values are shown in Figure 2. In the control challenge all values except that at 3 h after challenge were significantly lower than the pre-test values. No values are given for 4 hours and later for the control challenge because some patients had to be treated for severe bronchospasm. When the patients had been pretreated with budesonide for one week there was a significant fall ($p < 0.05$) after 5–60 min compared with the pre-test value, but the fall was significantly decreased compared with the control from 15–60 min and at 3 h ($p < 0.05$). After budesonide treatment for four weeks there was still a significant fall from 5–30 min after provocation compared with the pre-test value ($p < 0.05$), but the fall was significantly less compared with the control challenge from 5–60 min ($p < 0.05$). There was also a significantly lower fall than after budesonide treatment for one week at 10, 15, 20 and 60 min ($p < 0.05$).

Table 2.

Decrease in area under curve (AUC) from 0–60 min after challenge ($M \pm SEM$, $n = 10$).

	Control	Budesonide 1 + 1 mg	Budesonide 1 mg/day for seven days
Decrease in AUC (1)	6 552 $\pm$ 965	5 690 $\pm$ 932	4 699 $\pm$ 1 243
Relative change	1	0.91 $\pm$ 0.14	0.72 $\pm$ 0.19

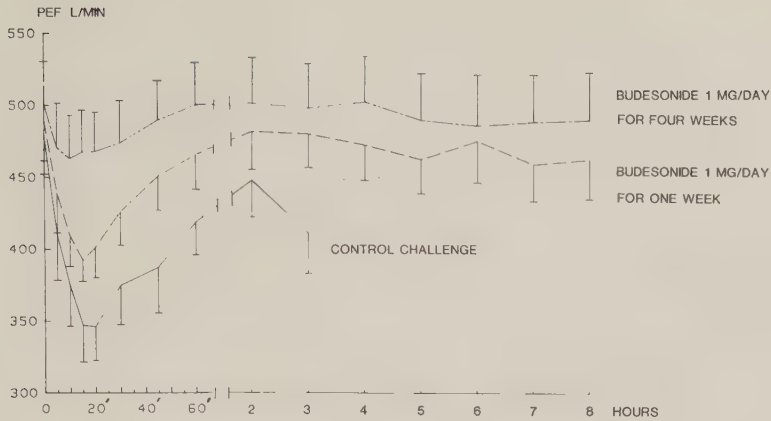


Figure 2.

Mean PEF $\pm$ SEM (l/min) from 0 to 8 hours after control challenge and after pretreatment with budesonide for one and four weeks ($n = 10$).

The mean maximum response after challenge is shown in Table 3. The values after challenge are all lower than the pre-test values. Regarding the immediate reaction budesonide treatment gave significant protection and four weeks' treatment was significantly better than treatment for one week.

Figure 3 shows the individual and mean response for the immediate reaction. The influence of the duration of treatment in almost all patients is obvious. The area under curve (AUC) was investigated for the immediate reaction during 0–60

Table 3.

PEF-values before and maximum response after bronchial challenge with allergen ($M \pm SEM$, $n = 10$).

Treatment	Prevalue PEF l/min	Immediate reaction PEF l/min	% in fall in PEF	Late reaction PEF l/min	% in fall in PEF
Control	479 $\pm$ 27	*** 333 $\pm$ 24	*** 30.8 $\pm$ 3.2	*** 282 $\pm$ 26	*** 40.9 $\pm$ 4.3
Budesonide one week	490 $\pm$ 28	*** 378 $\pm$ 18	***a 21.9 $\pm$ 3.3	**aaa 435 $\pm$ 26	**aaa 10.8 $\pm$ 2.7
Budesonide four weeks	501 $\pm$ 30	***aaa,b 452 $\pm$ 30	***aaa,bb 10.2 $\pm$ 2.1	**aaa 475 $\pm$ 33	**aaa 5.7 $\pm$ 1.5

** $p < 0.01$ Diff v pre-values

*** $p < 0.001$

a $p < 0.05$ Diff v control

aaa $p < 0.001$

b $p < 0.05$ Diff v bud one week

bb $p < 0.01$

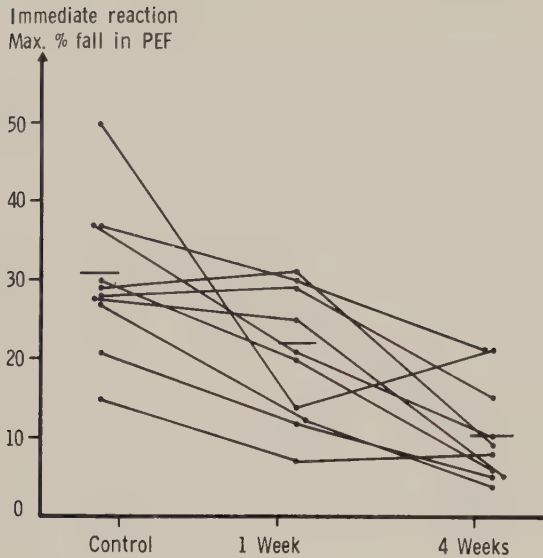


Figure 3.

Individual and mean maximum fall in PEF (%) during the immediate allergic reaction after control challenge and after one and four weeks pretreatment with budesonide.

min as in study 1. The decrease in area was significantly smaller after one and four weeks' treatment with budesonide than for the control challenge (Table 4). Four weeks' treatment was also better than one week's. Also regarding the late reaction both pretreatments offered a significant protection, but the difference between them was not significant (Table 3).

Table 4.

Decrease in area under curve (AUC) 0–60 min after challenge ($M \pm SEM$, $n = 10$).

	Control	Budesonide 1 mg/day for one week	Budesonide 1 mg/day for four weeks
Decrease in AUC (I)	5 400±691	** 3 597±741	*** ^{aa} 1 264±355
Relative change	1	0.67±0.14	0.23±0.07

** $p < 0.01$ Diff v control

*** $p < 0.001$

^{aa} $p < 0.01$ diff v budesonide for one week

DISCUSSION

It is widely thought that corticosteroids have no influence on the immediate allergic reaction, but inhibit the late reaction. Corticosteroids have nevertheless been used in the treatment of allergic diseases, including pure IgE-mediated reactions, such as pollen allergy.

The inhibitory effect of a glucocorticoid on the immediate bronchial reaction found in the present study is in accordance with previous results (3, 17, 26). However, in the study by van der Star et al (26) the authors were not convinced that beclomethasone dipropionate had any effect on the immediate reaction. The protective effect on the immediate reaction may be explained by the finding that glucocorticoids inhibit histamine release from human basophils and lower the histamine content in blood (25), inhibit histamine release from human lung (18), reduce the number of basophilic cells in nasal smear (20), decrease the activity of IgE-binding factor (29) and inhibit the IgE-mediated anaphylaxis in guinea pig lung (1).

The present study showed an additional effect of prolonged treatment. The result could have been influenced by the tendency to improved lung function, as reflected by the increase in PEF during the trial. But this change was neither statistically significant nor impressive (about 5 % after four weeks' treatment compared with the control). It is therefore not likely that this was the main cause for the decreased response. Another mechanism that may have influenced the response is that the treatment with inhaled budesonide caused a decrease in bronchial hyperreactivity. However, no consistent information is available regarding the effect of glucocorticoids on airway hyperreactivity (7, 13).

The findings in the present studies did not corroborate those of Pepys et al (21, 22, 23) and Booij-Noord et al (5), who did not find any effect of corticosteroids on the immediate reaction. A possible explanation for this discrepancy may be that Pepys et al used a pretreatment period of only 30 min before challenge. It has been shown that the effects of corticosteroids have a lag of some hours (8, 9). Booij-Noord et al (5) treated their patients with a daily dose of 15–20 mg prednisolone per os for 9 to 16 days before the challenge, but although there may have been an effect in some of the patients they did not find any decrease in the mean values for the immediate reaction. A contributory cause of the lack of effect may be that the patients were hospitalized because of obstructive disease whereas the patients in our study were out-patients with normal or virtually normal lung function. Another factor of importance may be that Booij-Noord et al induced a deeper fall in lung function in the control challenge, with an average of about 45 % (FEV₁) whereas the fall in the study by Martin (17) was 33 % (FEV₁) and about 30 % (PEF) in our study. A further possibility may be that oral corticosteroids are less effective in decreasing the immediate reaction and that the effect in the study by Martin et al (17) might be explained by the use of a large oral dose.

A finding that we have in common with Booij-Noord et al was that after the immediate reaction the PEF values returned to the pre-test values within 2 hours when the patients had been pretreated with corticosteroids. This did not occur in the control challenges when the patients were off treatment.

The late allergic reaction was also influenced by the duration of treatment, but even short pre-treatment had a marked beneficial effect. Prolonged treatment thus had but less additional effect on the late reaction than on immediate reaction although this increased efficacy was not without clinical importance. It is not possible from the results in this trial to say whether the late reaction was completely blocked after four weeks' treatment with budesonide because there was a significant fall after challenge compared with the pre-test values (Table 3). These clinically insignificant changes may also be caused by normal diurnal variation (14). That glucocorticosteroids are effective against late allergic reaction may be explained by decreased synthesis of mediators (leucotrienes, SRS-A) (4) and chemotactic factors (10). Such a view is supported by the findings by Forsberg and Sörenby (12) who found that budesonide decreased the release of SRS-A from sensitized guineapig lung after challenge.

REFERENCES

1. Andersson P, Brattsand R, Brange C, Källström L, Stahre G. Protective effects of budesonide on lung anaphylaxis in actively sensitized guinea pigs. Inhibition of "IgE"-mediated anaphylaxis. *Eur J Respir Dis* 1982; Suppl 122: 260-262.
2. Balle V H. The effect of budesonide in perennial rhinitis. *Eur J Respir Dis* 1982; Suppl 122: 197-204.
3. Burge P S. The effects of corticosteroids on the immediate asthmatic reaction. *Eur J Respir Dis* 1982; Suppl 122: 163-166.
4. Burka J F, Flower R J. Effects of Modulators of Arachidonic Acid Metabolism on the Synthesis and Release of Slow-Reacting Substance of Anaphylaxis. *Br J Pharmacol* 1979; 65: 35-41.
5. Booij-Noord H, Orie N G M, de Vries K. Immediate and late bronchial obstructive reactions to inhalation of house dust and protective effects of disodium cromoglycate and prednisolone. *J Allergy Clin Immunol* 1971; 48: 344-354.
6. Booij-Noord H, de Vries K, Sluiter H J, Orie N G M. Late bronchial obstructive reaction to experimental inhalation of house dust extract. *Clin Allergy* 1972; 2: 43-61.
7. Easton J G. Effect of an inhaled corticosteroid on methacholine airway reactivity. *J Allergy Clin Immunol* 1981; 67: 388-390.
8. Ellul-Micallef R, Hansson E, Johansson S Å. Budesonide: A new corticosteroid in bronchial asthma. *Eur J Respir Dis* 1980; 61: 167-173.
9. Ellul-Micallef R, Fenech F F. Intravenous prednisolone in chronic bronchial asthma. *Thorax* 1975; 30: 312-315.
10. Fauci A S, Dale D C, Balow J E. Glucocorticosteroid therapy: Mechanisms of action and clinical considerations. *Ann Intern Med* 1976; 84: 304-315.
11. Fawcett I W, Merchant J A, Simmonds S P, Pepys J. The effect of sodium cromoglycate, beclomethasone dipropionate and salbutamol on the ventilatory response to cotton dust in mill workers. *Br J Dis Chest* 1978; 72: 29-38.
12. Forsberg K, Sörenby L. The influence of a new corticosteroid, budesonide, on anaphylactic bronchoconstriction and SRS-A release in the guineapig. *Agents Actions* 1981; 11: 391-395.
13. Hartley J P R. Corticosteroid Aerosols and Airway Challenge. In: *Topical Steroid treatment for Asthma and Rhinitis*. Mygind N, Clark T J H, eds. Balliere Tindall, London 1980: 48-65.
14. Hetzel M R. The pulmonary clock. (Editorial) *Thorax* 1981; 36: 481-486.
15. Herxheimer H. The late bronchial reaction in induced asthma. *Int Arch Allergy Appl Immunol* 1959; 3: 323.
16. Johansson S Å, Andersson K E, Brattsand R, Hedner P, Gruvstad E. Topical and systemic glucocorticoid potencies of budesonide and beclomethasone dipropionate in man. *Eur J Clin Pharmacol* 1982; 22 (In press).

17. Martin G L, Atkins P C, Dunskey E H, Zweiman B. Effects of theophylline, terbutaline and prednisone on antigen-induced bronchospasm and mediator release. *J Allergy Clin Immunol* 1980; 66: 204–212.
18. Morr H, Bornemann G. Effect of glucocorticosteroids on histamine release from human lung in vitro. *Allergologie* 1980; 4: 237–239.
19. Munch E, Weeke B, Johansson S Å. The effect of budesonide on nasal allergen challenge in patients with seasonal rhinitis and on nasal peak flow in healthy volunteers. *Eur J Respir Dis* 1982; Suppl 122: 176–184.
20. Okuda M, Senba O. Effects of beclomethasone dipropionate nasal spray on subjective and objective findings in perennial allergic rhinitis. *Clin Otolaryngol* 1980; 5: 315–321.
21. Pepys J. Immunopathology of allergic lung disease. *Clin Allergy* 1973; 3: 1–22.
22. Pepys J, Davies R J, Breslin A B X, Hendrik D J, Hutchcroft B J. The effects of inhaled beclomethasone dipropionate (Becotide) and sodium cromoglycate on asthmatic reactions to provocation tests. *Clin Allergy* 1974; 3: 13–24.
23. Pepys J. Effects of inhaled beclomethasone dipropionate on bronchial provocation test reactions. *Postgrad Med J* 1975; 51 (Suppl 4): 42–48.
24. Pipkorn U: The effect of budesonide on the immediate reaction to allergen challenge – a rhinomanometric study. *Eur J Respir Dis* 1982; Suppl 122: 185–191.
25. Saavedra-Delgado A M P, Mathews K P, Pan P M, Kay D R, Muilenberg M L. Dose-response studies of the suppression of whole blood histamine and basophil counts by prednisone. *J Allergy Clin Immunol* 1980; 66: 464–471.
26. van der Star J G, Berg C W, Steenhuis C J, de Vries K. The effect of aerosol administration of beclomethasone dipropionate on reactive bronchial obstruction after inhalation of house dust. *Ned T Geneesk* 1976; 120: 45: 1928–1932.
27. Thalén A, Brattsand R. Synthesis and anti-inflammatory properties of budesonide, a new non-halogenated glucocorticoid with high local activity. *Arzneim-Forsch/Drug Res* 1979; 29: 1687–1690.
28. Willey R F, Godden D J, Carmichael J, Preston P, Frame M, Crompton G K. Comparison of twice daily administration of a new corticosteroid budesonide with beclomethasone dipropionate four times daily in the treatment of chronic asthma. *Br J Dis Chest* 1982; 76: 61–68.
29. Yodoi J, Hirashima M, Ishazaka K. Lymphocytes bearing Fc receptors for IgE. VI. Suppressive effect of glucocorticoids on the expression of Fc receptors and glycosylation of IgE-binding factors. *J Immunol* 1981; 127: 471–476.

Requests for reprints:

Dr R Dahl
 Department of Lung Medicine
 Århus Kommunehospital
 DK-8000 Århus
 Denmark

III

Budesonide: A new corticosteroid in bronchial asthma

R. ELLUL-MICALLEF, E. HANSSON & S. Å. JOHANSSON

Department of Medicine, University of Kuwait, and Research and Development Department
AB Draco*, Lund, Sweden

Abstract: The time course of response to budesonide in a dose of 1000 µg administered by inhalation, 800 µg given by the oral route, and 40 mg prednisolone administered orally, has been investigated in 12 patients suffering from chronic bronchial asthma. Budesonide is an epimeric mixture of a non-halogenated glucocorticoid, 16α, 17α-(22R,S)-propylmethylenedioxypregna-1,4-diene-11β,21-diol-3,20-dione. Inhaled budesonide and prednisolone produced a statistically significant increase in PEF 2 h after being administered. The peak effect appeared to occur between 6 and 7 h after budesonide inhalation and about 9 h following prednisolone. When given orally, budesonide failed to produce any substantial changes in PEF.

Résumé: L'évolution de la réponse dans le temps, au budesonide, administré en aérosol à la dose de 1000 µg ou per os à la dose de 800 µg, et à la dose de 40 mg de prednisolone per os, a été étudiée chez 12 patients atteints d'asthme bronchique chronique. Le budesonide est un mélange épimérique d'un glucocorticoïde non halogène, 16α, 17α-(22R,S)-propylmethylenedioxypregna-1,4-diene-11β,21-diol-3,20-dione. Le budesonide en inhalation et la prednisolone, ont provoqué une augmentation statistiquement significative du débit expiratoire de pointe 2 h après l'administration. Le pic de l'effet survient 6 à 7 h. après l'inhalation de budesonide, et environ 9 h. après la prise de prednisolone. En administration orale, le budesonide ne provoque pas d'augmentation substantielle du débit expiratoire de pointe.

Key words: bronchial asthma - glucocorticoids - inhaled budesonide - oral budesonide - oral prednisolone - time course of response.

Submitted in original form 1979-06-21

The value of corticosteroids in the management of bronchial asthma is now well established. The introduction of corticosteroid aerosols has proved to be a major advance in the treatment of this condition, allowing for a reduction or total withdrawal of oral corticosteroids (3,14). The time

course of response to a number of corticosteroids administered by both the oral (7,9) and intravenous (6,8) routes in chronic asthmatics has been worked out. However, no such work has so far been carried out on corticosteroids delivered by aerosol.

This study has been designed firstly to investigate the time course of response to budesonide, administered by aerosol in-

* Subsidiary of AB Astra, Sweden.

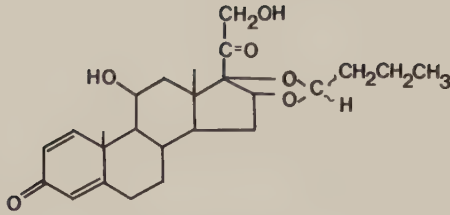


Figure 1. Structure of budesonide.

halation to patients with stable chronic bronchial asthma, and to compare it with oral prednisolone. Secondly, to try to determine whether an equivalent dose of budesonide given orally would result in the same pulmonary function changes in chronic asthmatics when administered by inhalation.

Budesonide (16 α ,17 α -(22R, S)-propylmethylenedioxypregna-1,4-diene-11 β ,21-diol-3,20-dione) is an epimeric mixture of a new synthetic non-halogenated glucocorticoid (Fig. 1). It has been shown to be about 2–3 times more potent than beclomethasone

dipropionate and fluocinolone acetonide in dermal vasoconstriction tests in man (Gruvstad, personal communication). It appears to be a corticosteroid with a high local activity and low systemic effect (20), and therefore a promising drug in the treatment of asthma.

PATIENTS AND METHODS

Twelve patients suffering from chronic bronchial asthma participated in this study. For the purpose of this study, chronic bronchial asthma is defined as a condition in which widespread reversible airway obstruction is present for a prolonged period with or without brief spontaneous remissions. Informed consent was obtained from all patients. Individual patient data are summarized in Table 1. Only patients with an FEV₁ $\leq$ 70% of predicted value were admitted to the study. They were not adequately controlled by existing treatment

TABLE 1. Individual patient data

Pt	Sex	Age	Type of asthma	Duration of asthma (yrs)	Predicted FEV _{1.0} (ml)	Part I		Part II	
						Initial FEV _{1.0}	Post broncho- dilator aerosol FEV _{1.0}	Initial FEV _{1.0}	Post broncho- dilator aerosol FEV _{1.0}
1.	F	50	intrinsic	6	2050	1400	1650	1250	1725
2.	M	44	extrinsic	34	3350	2250	2700	2350	2650
3.	F	54	intrinsic	8	1850	1350	1575	1100	1325
4.	F	47	extrinsic	22	2000	1300	1625	1625	2050
5.	F	48	extrinsic	36	1850	1250	1450	1325	1750
6.	M	17	extrinsic	10	4000	2650	3100	2975	3350
7.	M	41	extrinsic	21	3100	2050	2500	1825	2250
8.	M	23	extrinsic	20	3850	2425	3000	2200	2750
9.	M	34	extrinsic	22	3650	2500	3150	2850	3325
10.	M	32	extrinsic	24	3900	2300	2750	2600	3250
11.	F	46	intrinsic	3	2200	1450	1750	1250	1575
12.	M	35	extrinsic	30	4100	2900	3375	3250	3625

and all showed a fair degree of stability in their condition. The patients showed a 15–25% increase in FEV₁ following the use of salbutamol aerosol. None of the patients had ever had corticosteroids before. During the study they received no drugs other than the ones under test. Care was taken to ensure that no barbiturates or other enzyme-inducing agents were taken prior to the study.

Skin tests, chest roentgenogram, electrocardiogram, liver function tests, absolute eosinophil count and bacteriological sputum examination were performed in all patients. All nine extrinsic asthmatic patients had positive skin tests to a wide variety of allergens and blood eosinophilia. All electrocardiograms were normal. The chest roentgenograms were normal except for some hyperinflation. No pathogenic organisms were detected in sputum and the liver function tests were normal.

The first part of the study was designed as a double-blind trial in which each patient was studied over a 5-day period. On days 1, 3, 5, the patients were given placebo tablets and a placebo inhaler and on days 2 and 4 the patients were given, in a random fashion, either 40 mg prednisolone orally in a single dose and a placebo inhaler or placebo tablets and an inhaler containing budesonide. The total dose of budesonide was 1000 µg given in five metered doses. The relatively high doses of both budesonide and prednisolone were chosen to ensure detection of a measurable response.

An Air Med peak flow gauge was used to detect changes in pulmonary function. Prior to the study, the patients were shown how to use the instrument and record their results. Previous work had shown that PEF was a sensitive and reliable index of change in bronchial asthma (7). The best of three successive attempts over a 3-min period was

chosen and recorded. Both parts of the study were carried out in the patients' home on an out-patient basis. Drugs and placebos were administered each morning at 8 a.m. immediately after recording the first PEF. The procedure was repeated at hourly intervals over a 12-h period.

The inhaler was furnished with a tube (length 100 mm, diameter 32 mm) to diminish oral impaction. Previous evidence has shown that drug deposition in such an aerosol delivery system was not less than 20% of the delivered dose and that about 80% of the delivered dose would reach the patient. Investigations on deposition of terbutaline have been published by Morén (13) and confirmed for budesonide (Johansson, unpublished data). It was therefore decided to use a 20% smaller dose (800 µg) in the second part of the study. This part of the study was designed as a single blind trial, in which each patient served as his own control, and was carried out shortly after the first part. Patients swallowed one gelatine capsule at 8 a.m. every day over a 3-day period. The capsule contained lactose on day 1 and day 3, and 800 µg budesonide on day 2.

Statistical significance has been tested for by means of Student's *t*-test (19).

RESULTS

No patient manifested any untoward side effects to any of the drugs given. The initial degree of airway obstruction in the patients did not differ significantly in the two parts of the study. Very little diurnal variation was observed during the placebo days. No response to the placebo tablets, capsules, or placebo inhaler, could be demonstrated in the patients individually or the group as a whole. To avoid residual effects of the active treatments, the data from the first placebo days were chosen for comparison.

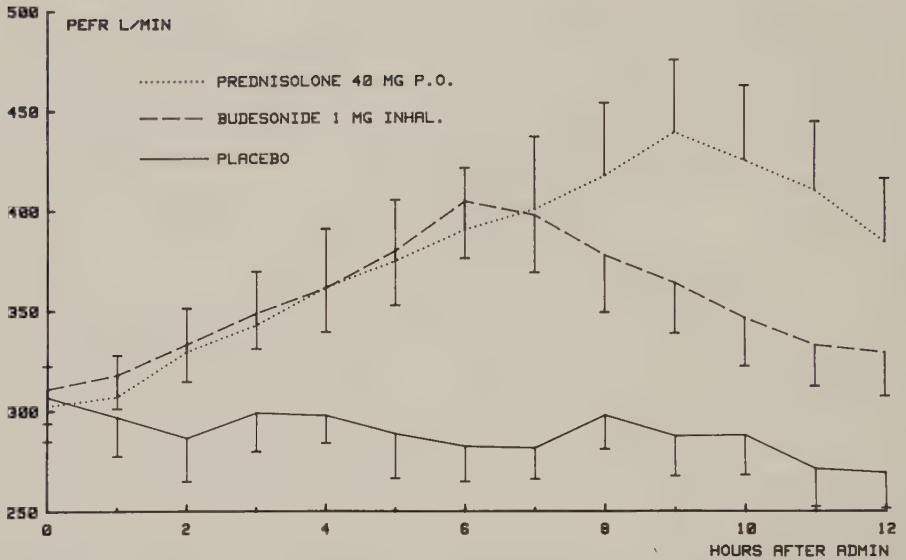


Figure 2. Effect of a single dose of 40 mg prednisolone, 1 mg budesonide by inhalation and placebo tablets on PEF. Group mean values $\pm$ SEM are shown for 12 patients. Pre-treatment values for budesonide and prednisolone were 311 ± 17 and 303 ± 20 l/min (Mean $\pm$ SEM) respectively.

Oral prednisolone and inhaled budesonide produced consistent improvement in PEF in eight of the 12 patients studied.

Three patients, Nos. 4, 5, and 8, failed to show any response to either drug, whilst patient No. 9 improved when given pred-

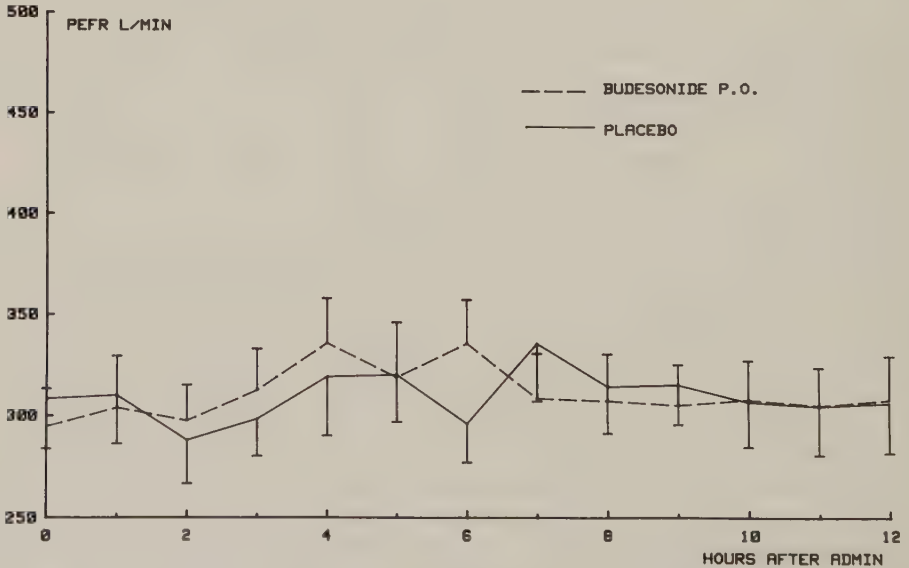


Figure 3. Effect of a single oral dose of 800 μ g budesonide and placebo tablets on PEF. Group mean values $\pm$ SEM are shown for 12 patients.

nisolone but showed no response to inhaled budesonide. Fig. 2 shows the time course of response to inhaled budesonide and oral prednisolone in the 12 asthmatic patients. The peak effect appeared to occur between 6 and 7 h after budesonide inhalation and about 9 h following prednisolone administration. Changes in PEF were statistically significant when compared with placebo and initial values from 2 h after the administration of both budesonide and prednisolone ($P < 0.001$). With inhaled budesonide, the changes in PEF values were significant up to 12 h ($P < 0.01$) whilst with prednisolone, the changes were still significant up to 27 h ($P < 0.05$) after the drug had been given. Individual peaks ranged between 6 and 8 h following budesonide administration and between 8 and 10 h after prednisolone. When the effect of the two drugs on PEF was compared, it was seen that oral prednisolone produced a statistically significant greater response from the 8th hour onwards following drug administration. Oral prednisolone also resulted in a significantly greater maximum response in PEF ($P < 0.01$).

The effect on the PEF values following oral budesonide and placebo is shown in Fig. 3. Statistically significant differences from the immediate pre-treatment value were observed at 4 h ($P < 0.001$) and 6 h ($P < 0.01$) after drug administration. There was also a statistically significant difference between budesonide and placebo at 6 h ($P < 0.05$). The difference was 39.6 ± 13.1 l/min (Mean $\pm$ SEM).

DISCUSSION

The changes in pulmonary function following the administration of a drug in the treatment of bronchial asthma seem to be related not only to the initial degree of

airway obstruction (11) but, and perhaps even more important, also to the path of improvement or deterioration by which the initial stage of airway obstruction had been reached (16). Although variations were present in the initial values of FEV₁ when budesonide was first given by inhalation and when administered orally, such changes were small and not statistically significant ($P < 0.5$). In fact, when the drug was inhaled the initial values ranged between 1.25 l and 2.90 l (1.98 ± 0.17 l, Mean $\pm$ SEM) and when given orally they ranged between 1.10 l and 3.25 l (2.05 ± 0.20 , Mean $\pm$ SEM). The initial degree of reversibility to salbutamol shown by the patients on the two separate occasions was also very similar. The differences in changes produced by salbutamol in the two studies were also not statistically significant ($0.5 < P < 0.1$). The lack of response to oral budesonide cannot therefore be attributed to a different initial degree of airway obstruction.

No real improvement could be detected in PEF measurements in individual patients when given budesonide orally. We do not consider the mean results obtained at 12 a.m. and 2 p.m. on the days when the patients were on oral budesonide to be of any actual clinical relevance. It is known that only about 10–25% of the total amount of a drug given by inhalation actually reaches the lungs (4, 12), the rest is swallowed having been deposited in the mouth directly, or as a result of mucociliary clearance, and may be absorbed from the gastrointestinal tract (5, 15). In spite of the uneven distribution because of widespread airway obstruction just such a small amount of inhaled budesonide was responsible for a therapeutic effect; this did not occur when the corticosteroid was administered orally.

Drug absorption from the lungs can

occur very rapidly (1,17). There is evidence of rapid pulmonary absorption of tritium labelled beclomethasone dipropionate in both rat and dog (12). It seems that only a small amount of corticosteroid need reach the target tissue in order to produce a biological effect (10).

There is no explanation for the result observed in patient No. 9. This 34-year-old extrinsic asthmatic male patient had the same degree of airway obstruction as the other patients. Prednisolone was the first active drug he received and it produced a maximum increase in PEF of 43% (160 l/min) over the immediate pre-treatment value. This improvement completely disappeared after 24 h. When asked to demonstrate he was found to use the inhaler correctly.

In the patients responding to the drug, there was a general trend for budesonide to product its peak effect 1-3 h earlier but then to lose its effect sooner than prednisolone. Oral prednisolone consistently resulted in higher peak effects in PEF than did inhaled or oral budesonide. The maximum effects produced by budesonide aerosol resulted in an increase of 32%-70% of the immediate PEF pre-treatment values. Such results may be the effect of differences in the metabolism of the two drugs, and perhaps also because different routes of administration were employed. The latter need not necessarily be the reason for the difference in the time course of response between the two drugs (8). A direct relationship between the absorption of corticosteroids and their biological activity does not seem to be necessary (18). The duration of the effect of the drugs administered is perhaps influenced by the degree of peak effect achieved. Both drugs had a similar time lag before an improvement in the patient's condition was detected. It may well be that this is the

time needed for the corticosteroids to be transported to the target tissue, bound to the specific cytoplasmic receptors, and then translocated to the nucleus in an 'activated' form and bound to the target cell genomes, after which intra-cellular and protein synthesis transcription can eventually take place (2).

REFERENCES

1. Burton J. A, Schanker L S. Pulmonary absorption of aerosolized solutes. *Fed Proc* 1971; 30: 447.
2. Chan L, O'Malley B W. Steroid hormone action: Recent advances. *Ann Int Med* 1978; 89: 694-701.
3. Clark T J H. Effect of beclomethasone dipropionate delivered by aerosol in patients with asthma. *Lancet* 1972; i: 1361-1364.
4. Davies D S. Pharmacokinetics of inhaled substances. *Scand J Respir Dis* 1978; Suppl. 103: 44-49.
5. Dollery C T, Davies D S, Conolly M E. Differences in the metabolism of drugs depending upon their routes of administration. *Ann NY Acad Sci* 1971; 179: 108-111.
6. Ellul-Micallef R. The time course of response to corticosteroids in bronchial asthma. Ph.D. Thesis, University of Edinburgh, 1972.
7. Ellul-Micallef R, Borthwick R C, McHardy G J R. The time course of response to prednisolone in chronic bronchial asthma. *Clin Sci Mol Med* 1974; 47: 105-117.
8. Ellul-Micallef R, Fenech F F. Intravenous prednisolone in chronic bronchial asthma. *Thorax* 1975; 30: 312-315.
9. Ellul-Micallef R, Fenech F F, Parrot D. Comparison of clocyprednol and prednisolone in chronic asthmatic patients. *Br J Clin Pharmacol* 1978; 6: 91-93.
10. Fotherby K, James F. Advances in steroid biochemistry and pharmacology. Vol. 3. New York: Academic Press, 1972: 67-165.
11. Hume K M, Gandevia B. Forced expiratory volume before and after isoprenaline. *Thorax* 1957; 12: 276-279.
12. Martin L E, Harrison C, Tanner R J N. Metabolism of beclomethasone dipropionate by animals and man. *Postgrad Med J Suppl* 4 1975; 51: 11-20.
13. Morén F. Drug deposition of pressurized inhalation aerosols. *Int J Pharm* 1978; 1: 205-212.

14. Morrow Brown H, Storey G, George W H S. Beclomethasone dipropionate: A new steroid aerosol for the treatment of allergic asthma. *Br Med J* 1972; 1: 585-590.
15. Nilsson H T, Simonsson B G, Ström B. The fate of ³H-terbutaline sulphate administered to man as an aerosol. *Eur J Clin Pharmacol* 1976; 10: 1-7.
16. Pain M C F, Read J. Patterns of response to bronchodilator in young patients with asthma. *Austr Ann Med* 1963; 12: 216-220.
17. Schanker L S. Drug absorption from the lung. *Biochem Pharmacol* 1978; 27: 381-385.
18. Schedl H P. Absorption of steroid hormones from the human small intestine. *J Clin Endocrinol Metab* 1965; 25: 1300-1312.
19. Snedecor G W, Cochran W G. Statistical methods, 6th ed. Ames, Iowa: Iowa State University Press 1971.
20. Thalén A, Brattsand R. Synthesis and anti-inflammatory properties of budesonide, a new non-halogenated glucocorticoid with high local activity. *Arzneim Forsch Drug Res* 1979; 29: 1687-1690.

Address:

Dr. R. Ellul-Micallef
Department of Medicine
P.O. Box 24923 Safat
University of Kuwait
Kuwait
Arabia

IV

ACUTE DOSE-RESPONSE STUDIES IN BRONCHIAL ASTHMA WITH A NEW CORTICOSTEROID, BUDESONIDE

R. ELLUL-MICALLEF¹ & S.A. JOHANSSON²

¹Department of Pharmacology, University of Kuwait, Kuwait and ²Medical Department, AB DRACO, Lund, Sweden

- 1 Budesonide is an epimeric mixture of a new synthetic non-halogenated glucocorticoid (16 α , 17 α ,-(22R,S)-prophylmethylenedioxypregna-1,4-diene-11/3,21-diol-3,20-dione).
- 2 Acute dose response studies with three different inhaled doses of budesonide, have been carried out in a group of 12 chronic asthmatic patients.
- 3 The lowest dose (100 μ g) of inhaled budesonide produced a more marked effect in relieving airflow obstruction, than a much larger (1600 μ g) oral dose of the drug.
- 4 When the area under the curve for peak expiratory flow rate values was calculated, a dose-response relationship could be seen between the different inhaled doses.
- 5 It appears that budesonide has a predominantly local anti-asthmatic action in the lung.

Introduction

Budesonide (16 α , 17 α ,-(22R,S)-prophylmethylenedioxypregna-1,4-diene-11 β ,21-diol-3,20-dione) is an epimeric mixture of a new synthetic non-halogenated glucocorticoid. Animal studies show it to have high local and low systemic activity (Thalén & Brattsand, 1979). In man it has recently been shown that budesonide has a higher topical anti-inflammatory and a lower systemic effect than beclomethasone dipropionate, both after oral and aerosol administration (Johansson *et al.*, 1982). This seems to be due to the fact that budesonide undergoes an extensive and rapid biotransformation in the liver (Andersson *et al.*, 1983). Unlike beclomethasone dipropionate, budesonide is not metabolised in the lung (Martin *et al.*, 1974; Hartiala *et al.*, 1979; Ryrfeldt *et al.*, 1983). Budesonide thus appears to be a promising drug in the treatment of bronchial asthma.

We investigated the time course of response to budesonide, administered both by aerosol inhalation and orally in a group of patients with chronic bronchial asthma (Ellul-Micallef *et al.*, 1980b). The drug has since been further studied and favourably reported on in asthma (Willey *et al.*, 1981), rhinitis (Balle *et al.*, 1980; Pipkorn *et al.*, 1980; Malm *et al.*, 1981) and in psoriasis (Agrup *et al.*, 1981).

The present study was undertaken to establish whether acute dose-response studies with inhaled corticosteroids could be carried out in a group of very carefully selected patients with chronic bronchial

asthma. At the same time an attempt has also been made to monitor the effect on airflow obstruction of much lower doses of inhaled budesonide than those used in our previous study in an attempt to determine a therapeutic dose range.

Methods

Twelve patients, six males and six females, suffering from chronic bronchial asthma participated in the study. Five suffered from intrinsic asthma, the rest being extrinsic asthmatics. The duration of asthmatic symptoms ranged from 1 to 25 years. Individual patient data are summarized in Table 1. For the purpose of this study, chronic bronchial asthma is defined as a condition in which widespread reversible airflow obstruction is present for a prolonged period of time with or without brief spontaneous remissions. Informed consent was obtained from all patients. Only patients with an FEV₁ < 80% of predicted normal value were admitted to the study. They were not adequately controlled by existing treatment and all showed a fair degree of stability in their condition. The patients showed a mean increase in FEV₁ of 23% (range 13-56%) 15 min after two inhalations from a pressurized salbutamol inhaler. Patients who had used corticosteroids during the 4 weeks preceding the study or suffered from any disease likely to interfere

Table 1 Data on twelve asthmatic patients

Patient	Age (years)	Sex	Duration (years)	Type	FEV ₁ (ml) (predicted)	FEV ₁ (ml) (initial)	FEV ₁ (ml) (post-salbutamol)
1	30	M	12	Ext.	3600	2550	2950
2	18	F	5	Ext.	3000	2250	2725
3	17	F	8	Ext.	2800	2200	2585
4	35	F	1	Int.	2750	1850	2250
5	46	M	3	Int.	3150	2150	2550
6	33	M	3	Int.	3800	2800	3300
7	37	F	25	Ext.	2650	1825	2250
8	35	M	11	Ext.	3700	2650	3000
9	38	F	4	Int.	2500	1750	2100
10	50	F	2	Int.	2350	1700	2650
11	41	M	22	Ext.	3350	2175	2700
12	22	M	10	Ext.	4000	2850	3550

Ext - extrinsic, int - intrinsic.

with the objective of the study such as other respiratory or hepatic diseases, or thyroid dysfunction as well as females who were pregnant, lactating or actively sought pregnancy were not admitted into the study.

In the first part of the study the patients received under single-blind conditions a single oral dose of 40 mg (0.11 mM) prednisolone phosphate on the first day and a placebo tablet on the second day. This was done to ensure that the patients were corticosteroid responders. Only patients who had an increase in their peak expiratory flow rate (PEFR) of at least 25% above the pretreatment value were admitted into the second half of the study.

The second part of the study was carried out under double-blind, cross-over conditions and performed during 4 consecutive days. The patients were then given, in a random fashion using a double dummy technique, inhaled budesonide in three different doses 100 µg, 400 µg and 1600 µg (0.23, 0.93 and 3.72 µM respectively) and 1600 µg of oral budesonide. All drugs and placebo were administered each morning as a single dose at 08.00 h immediately after recording the first PEFR. An Air Med Mini Meter was used to detect changes in airflow obstruction. Prior to the study the patients had been taught how to use the peak flow meter correctly and how to record their results. The best of three successive attempts was chosen and recorded. Spirometric tests were repeated at hourly intervals for a 12 h period. Statistical significance was tested in all instances by means of Student's *t*-test (Snedecor, 1971).

Results

None of the patients showed any untoward side-effects to any of the drugs given. All extrinsic asthmatic patients had evidence of a hypersensitivity

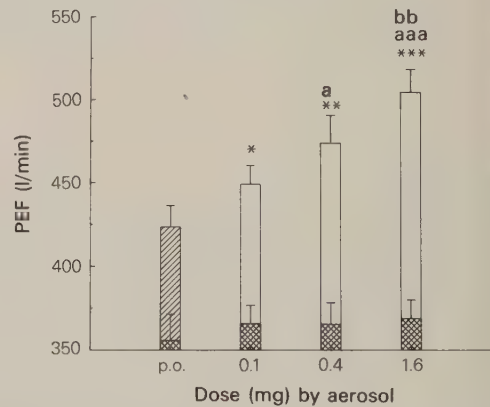


Figure 1 Mean $\pm$ s.e. mean maximum effect in PEF (l/min) by one oral (p.o.) and three inhaled doses of budesonide ($n = 12$).

* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ difference vs budesonide 1.6 mg p.o. a $P < 0.05$, aaa $P < 0.001$ difference vs budesonide 0.1 mg by inhalation. bb $P < 0.01$ difference vs budesonide 0.4 mg by inhalation.

The cross-hatched areas represent pretreatment mean maximum PEF + s.e. mean (l/min)

diathesis; positive prick skin tests to a wide variety of allergens and blood eosinophilia. Electrocardiogram graphs showed normal patterns in all patients except for patients 5 and 10 who had mild ischaemic changes. The chest radiographs were also normal except those of patients 7 and 11, which showed a moderate degree of hyperinflation. There was no clinical or bacteriological evidence of any chest infections. Initial PEFR values on the days in which prednisolone and inhaled budesonide were administered were not significantly different. The initial PEFR values for oral budesonide differed significantly from those of oral

prednisolone ($P < 0.05$), in spite of the small absolute difference in values, 16 ± 7 l/min (mean $\pm$ s.e. mean).

The maximum effect on PEFR produced by the different aerosol doses and the oral dose of budesonide is shown in Figure 1. All inhaled doses of budesonide produced a significantly greater increase in PEFR than did oral budesonide ($P < 0.05$; $P < 0.01$; $P < 0.001$). When the area under the curve for PEFR was calculated (Figure 2) a dose-response relationship could be seen between the different inhaled doses of budesonide. The smallest dose of inhaled budesonide ($100 \mu\text{g}$) was significantly more effective in relieving airflow obstruction than a markedly greater amount of oral budesonide ($1600 \mu\text{g}$).

The time course of response to oral prednisolone, oral budesonide and the three aerosol doses of budesonide is shown in Figure 3. The maximum increase in PEFR produced by 40 mg oral prednisolone was significantly greater than that produced by the different budesonide administrations ($P < 0.001$). The effect of prednisolone was still present during the second trial day which was used as a 'wash-out' day. However, it disappeared completely in all patients at the start of the second half of the study. A statistically significant increase in PEFR was produced 1 h after the inhalation of both $400 \mu\text{g}$ and $1600 \mu\text{g}$, in the group of patients as a whole ($P < 0.05$, $P < 0.001$). Oral budesonide and $100 \mu\text{g}$ inhaled budesonide produced a significant increase in PEFR 2 h after their administration, as did oral prednisolone ($P < 0.05$; $P < 0.01$; $P < 0.001$). The duration of effect of inhaled budesonide was 11 h with the highest dose and 10 h with the lower 2 doses. The effect of oral budesonide also lasted for 11 h.

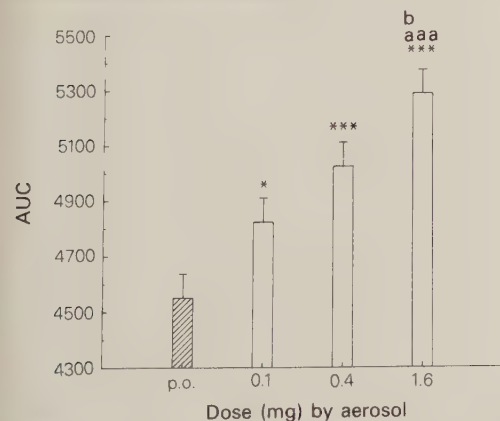


Figure 2 Mean area under curve (AUC) calculated on PEF for one oral and three inhaled doses of budesonide ($n = 12$).

* $P < 0.05$, *** $P < 0.001$ difference vs budesonide 1.6 mg p.o. aaa $P < 0.001$ difference vs budesonide 0.1 mg by inhalation. b $P < 0.05$ difference vs budesonide 0.4 mg by inhalation.

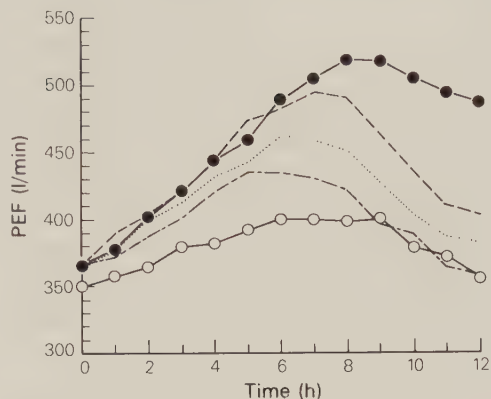


Figure 3 The time course of response (PEF, l/min) to oral prednisolone and budesonide in one oral and three inhaled doses. The range for s.e. mean was 9–22 l/min ($n = 12$).

●—● prednisolone 40 mg p.o., --- budesonide 1600 μg inhalation, budesonide 400 μg inhalation, ——— budesonide 100 μg inhalation, ○—○ budesonide 1600 μg p.o.

Discussion

A simple test of pulmonary function, PEFR was chosen to detect changes in airflow obstruction as previous work had shown it to be a sensitive and reliable index of change in bronchial asthma (Ellul-Micallef *et al.*, 1974). In monitoring the effects of a drug in this condition it is perhaps more meaningful to use an easy, simple test frequently rather than the occasional elaborate work-out in the laboratory. In order to increase the availability of the drug to the lung and diminish the amount of oropharyngeal deposition, a tube spacer was interposed between the inhaler and the mouthpiece before budesonide was administered (Morén, 1978). Asthmatic patients not infrequently find difficulties in using a pressurized aerosol efficiently (Saunders, 1965) even when taught how to use it (Patterson & Crompton, 1976). The altered airway deposition of drug particles produced by the tube spacer seems to benefit such patients (Ellul-Micallef *et al.*, 1980b; Godden & Crompton, 1981).

It was possible to carry out an acute dose-response study with single doses of inhaled budesonide in our group of asthmatic patients because of careful initial selection. Our group of patients suffered from chronic bronchial asthma and all displayed small diurnal variations in their PEFR measurements prior to admittance to the study. They were 'stable' in the sense that their PEFR at the start of the trial had not been recently arrived at via a path of improvement or deterioration in their airflow obstruction. In this study prednisolone was used as a tool to select suitable patients.

The various doses of inhaled budesonide resulted in statistically significant differences in the maximum response in PEFR. No significant difference could, however, be detected between the various time intervals needed to attain the different peak effects on PEFR values. The duration of the effect of the drug administered appears to be influenced by the degree of peak effect achieved. The study showed a linear relationship in the maximum increase in PEFR produced by the different inhaled doses of budesonide.

The lowest dose of inhaled budesonide produced a more marked physiological effect than a much larger ($\times 16$) oral dose of the drug. This seems to indicate that budesonide has a predominantly topical anti-asthmatic action in the lung. Budesonide is rapidly

absorbed through the mucosa of the respiratory tract and there is little or no biotransformation of the drug in the lung (Brattsand *et al.*, 1983). It appears that the swallowed portion of the drug has very little effect (Ellul-Micallef *et al.*, 1980a). These findings agree with those of Ryrfeldt and his co-workers (1981) who showed that oral budesonide had a bioavailability of only 11%. It is now known that most of the budesonide absorbed from the gastrointestinal tract is rapidly and extensively metabolized by the liver (Andersson *et al.*, 1983). The above mentioned findings and the fact that budesonide has a half-life of only about 2 h in man would explain why budesonide seems to have such a low potential for inducing systemic effects (Johansson *et al.*, 1983).

References

- AGRUP, G., BJÖRNBERG, A., ELMROS, T., GROTH, O., HANNUKSELA, H., LASSUS, A., SALDE, L., SKOGH, M. & THOMSEN, K. (1981). Clinical trial of a potent non-halogenated topical steroid, budesonide. *Acta Dermatovener.*, **61**, 180–182.
- ANDERSSON, P., EDSBÄCKER, S., RYRFELDT, A. & VON BAHR, C. (1983). *In vitro* biotransformation of glucocorticoids in liver and skin homogenate fraction from man, rat and hairless mouse. *J. steroid Biochem.*, **16**, (in press).
- BALLE, V., PEDERSEN, V. & ENGBY, B. (1980). Allergic perennial and non-allergic vasomotor rhinitis treated with budesonide nasal spray. *Rhinology*, **18**, 135–142.
- BRATTSAND, R., KÄLLSTRÖM, L., NILSSON, E., RYRFELDT, A. & TÖNNESSON, M. (1983). The deposition of budesonide in the lung in guinea pig and rat. *Eur. J. resp. Dis.*, Suppl. (in press).
- ELLUL-MICALLEF, R., BORTHWICK, R.C. & MCHARDY, G.J.R. (1974). The time course of response to prednisolone in chronic bronchial asthma. *Clin. Sci. mol. Med.*, **47**, 105–117.
- ELLUL-MICALLEF, R., HANSSON, E. & JOHANSSON, S.A. (1980a). Budesonide: A new corticosteroid in bronchial asthma. *Eur. J. resp. Dis.*, **61**, 167–173.
- ELLUL-MICALLEF, R., MORÉN, F., WETTERLIN, K. & HIDINGER, K.G. (1980b). Use of special inhaler attachment in asthmatic children. *Thorax*, **35**, 620–623.
- GODDEN, D.J. & CROMPTON, G.K. (1981). An objective assessment of the tube spacer in patients not able to use a conventional pressurized aerosol efficiently. *Br. J. dis. Chest*, **75**, 165–168.
- HARTIALA, J., VOTILA, P. & NIENSTEDT, W. (1979). Absorption and metabolism of intratracheally instilled cortisol and beclomethasone dipropionate in the isolated perfused rat lungs. *Med. Biol.*, **57**, 294–297.
- JOHANSSON, S.A., ANDERSSON, K.E., BRATTSAND, R., GRUVSTAD, E. & HEDNER P. (1983). Topical and systemic glucocorticoid potencies of budesonide, beclomethasone dipropionate and prednisolone in man. *Eur. J. resp. Dis.*, Suppl. (in press).
- MALM, L., WIHL, J.A., LAMM, C.J. & LINDQVIST, N. (1981). Reduction of metacholine-induced nasal secretion by treatment with a new topical steroid in perennial non-allergic rhinitis. *Allergy*, **36**, 209–214.
- MARTIN, L., TANNER, R.J.N., CLARK, T.J.H. & COCHRANE, G.M. (1974). Absorption and metabolism of orally administered beclomethasone dipropionate. *Clin. Pharmac. Ther.*, **15**, 267–270.
- MORÉN, F. (1978). Drug deposition of pressurized inhalation aerosols. *Int. J. Pharmac.*, **1**, 205–212.
- PATTERSON, I.C. & CROMPTON, G.K. (1976). Use of pressurized aerosols by asthmatic patients. *Br. med. J.*, **1**, 76–78.
- PIPKORN, U., RUNDCRANTZ, H. & LINDQVIST, N. (1980). Budesonide a new nasal steroid. *Rhinology*, **18**, 171–175.
- RYRFELDT, A., ANDERSSON, P., EDSBÄCKER, S., TÖNNESSON, M., DAVIES, D. & PAUWELS, R. (1983). Pharmacokinetics and metabolism of budesonide, a selective glucocorticoid. *Eur. J. resp. Dis.*, Suppl. (in press).
- SAUNDERS, K.B. (1965). Misuse of inhaled bronchodilator agents. *Br. med. J.*, **1**, 1037–1039.
- SNEDECOR, G.W. & COCHRAN, W.G. (1971). *Statistical methods*. Ames: Iowa State University Press.
- THALÉN, A. & BRATTSAND, R. (1979). Synthesis and anti-inflammatory properties of budesonide, a new non-halogenated glucocorticoid with high local activity. *Arzneim-Forsch/Drug Res.*, **29**, 1687–1690.
- WILLEY, R.F., GODDEN, D.J., CARMICHAEL, J., PRESTON, P., FRAME, M. & CROMPTON, G.K. (1982). Comparison of twice daily administration of a new corticosteroid budesonide with beclomethasone dipropionate four times daily in the treatment of chronic asthma. *Br. J. dis. Chest*, **76**, 61–68.

(Received July 15, 1982,
accepted October 29, 1982)

v

DOSE-FREQUENCY IN CHRONIC BRONCHIAL ASTHMA WITH A NEW CORTICOSTEROID BUDESONIDE

R Ellul-Micallef^{*} & S-Å Johansson^{**}

^{*} Department of Pharmacology, University of Kuwait and
Allergy Centre, Al-Sabah Hospital, Kuwait

^{**} Department of Clinical Research, AB Draco, Lund, Sweden

SUMMARY

Corticosteroid aerosols are an established form of treatment in bronchial asthma. The present study reports on the time course of response of 3 different dosage regimens of inhaled budesonide in chronic "stable" asthmatic patients. The patients were previously shown to be corticosteroid-responders. Budesonide given q.i.d. in 100 µg doses was seen to produce greater relief of airflow obstruction, as indicated by PEF measurements, than 400 µg given as a single morning dose. The highest dose of budesonide, 1600 µg, resulted in greater PEF values than the divided dose at 2, 4 and from 5 to 7 hours after administration. The divided dose was however superior from the tenth hour onwards. The present study shows that dosing frequency has an important effect on the relief of airflow obstruction in chronic bronchial asthma.

Key words: Budesonide, prednisolone, dosing frequency, chronic asthma, time course of response.

In spite of recent controversy regarding the hypothalamic-pituitary-adrenal effects of inhaled corticosteroids (Wyatt et al 1978; Kershmar et al 1978; Vaz et al 1982), the introduction of this form of treatment in the management of bronchial asthma may rightly be regarded as a therapeutic milestone. Budesonide (16 α , 17 α -(22R, S) propylmethylenedioxypregna-1, 4-diene-11 β , 21-diol-3, 20-dione) is a synthetic non-halogenated glucocorticoid with a high local and a low systemic activity. Recent studies have shown that budesonide has a higher topical anti-inflammatory and a lower systemic effect than beclomethasone dipropionate (Johansson et al 1982). Budesonide is known to undergo a rapid and extensive biotransformation in the liver and unlike beclomethasone dipropionate, is not metabolised in the lung (Ryrfeldt et al 1982). The drug has been favourably reported upon in a number of conditions, including asthma (Ellul-Micallef et al 1980), rhinitis (Malm et al 1980) and psoriasis (Agrup et al 1981).

The object of the present study was to investigate the time course of response and maximum effect of 1600 μ g and 400 μ g of inhaled budesonide given in a single dose at 8 a.m., comparing this with a multiple dose of 100 μ g inhaled budesonide.

PATIENTS AND METHODS

The study initially included twelve patients, seven males and five females, suffering from chronic bronchial asthma who all displayed small diurnal variations in their airflow obstruction. Eight patients had extrinsic asthma, the rest being intrinsic asthmatics. Individual patient data are summarized in TABLE 1. Informed consent was obtained in all patients. Only patients whose FEV₁ was less than 75% of their predicted normal values were admitted to the study. Prior to admittance to the study the patients had to exhibit at least 15% reversibility in their FEV₁ following 2 inhalations of salbutamol from a metered aerosol inhaler. Patients who had used corticosteroids during the 4 weeks preceding the study or who were on disodium cromoglycate were not included. Similarly, patients were excluded, if they suffered from any concomitant illness likely to interfere with the objective of the study, this comprised respiratory or hepatic diseases, as well as thyroid dysfunction. Females who were pregnant, lactating or actively sought pregnancy were also excluded. During the trial the patients were on no medications except for the drugs under study. All patients had an electrocardiograph, a chest radiograph, sputum bacteriological examination, a blood eosinophil count and were skin prick tested with a wide variety of allergens.

To ensure that the patients were corticosteroid responders, 40 mg (0.11 mM) prednisolone were administered orally in a single dose under single blind conditions on the second day of the study following placebo administration the previous day (Ellul-Micallef et al 1974). Improvement in airflow obstruction was monitored by means of an Air Med Mini Meter, the peak expiratory flow (PEF) being measured two hourly over a twelve hour period. Only patients showing an increase in their PEF of at least 20% above the pretreatment values were admitted to the second part of the study. The latter was performed under double-blind, cross-

over conditions and carried out over five consecutive days, two days after the administration of prednisolone. The different inhaled doses of budesonide were given in a randomized fashion on days 1, 3 and 5; days 2 and 4 being used as "wash out" days. Budesonide in single doses of 1600 μg and 400 μg were given each morning at 8 a.m.; 100 μg of budesonide being administered at 8 a.m., 10 a.m., noon and 2 p.m. All inhalations were given with an extended inhalation device (Inhalet^R). The PEF was this time recorded hourly over a twelve hour period. The best of three successive attempts was chosen and recorded. Statistical significance was tested in all instances by means of Student's t-test (Snedecor & Cochran 1971).

RESULTS

No patient manifested any untoward side-effects to any of the drugs given. Of the patients selected for the trial, patient no 2 dropped out because he developed an acute asthmatic attack on the day following prednisolone treatment. Electrocardiographs showed normal patterns in all patients. The chest radiographs were also normal, except for that of patient no 6, who showed a moderate degree of hyperinflation. There was no clinical evidence of any chest infection; bacteriological examination of the sputum failed to reveal any pathogenic organisms. All extrinsic asthmatic patients had evidence of a hypersensitivity diathesis as shown by positive prick-skin test reactions to a wide variety of allergens. The number of blood eosinophils in the extrinsic asthmatic patients ranged from 253 to $713 \times 10^6/l$, with a mean of $520 \times 10^6/l$ whilst intrinsic asthmatics had a range of 288 to $545 \times 10^6/l$ with a mean of $457 \times 10^6/l$.

The starting PEF values for all subjects varied somewhat between trial days. For each individual a reference PEF value was calculated as the mean of the values at 8 a.m. for all trial days. The mean and maximum deviations for any one day from this reference value was then calculated for each subject. The mean deviation between trial days was found to be 7.1% (5.9-8.2%) whilst the mean maximum deviation for each subject was 12.8% (10.3-15.4%). The difference between the starting PEF value for the different trial days was not statistically significant.

The effect of 40 mg (0.11 mM) prednisolone and placebo on the PEF in the eleven asthmatic patients who completed the study is shown in FIGURE 1. Prednisolone resulted in a mean maximum improvement in PEF of 42% (range 27-64%) on the initial PEF values. Patient no 2 who dropped out of the trial had an improvement of 26% in his PEF values. Prednisolone administration produced a significant increase in PEF at each time of measurement from 2 hours onwards ($p < 0.01$). Placebo did not have any significant effect.

The effect of the three different inhaled doses of budesonide is shown in FIGURE 2. When the three different modes of administration were compared it was seen that the highest dose of budesonide (1600 μg) resulted in PEF values that were statistically significantly higher than those produced by 400 μg budesonide at 1, 2, 4 and from 6 hours onwards ($p < 0.01$). When the divided dose of budesonide (100 $\mu\text{g} \times 4$) was compared with the highest dose the PEF values obtained were significantly higher from 10 hours onwards with the divided dose ($p < 0.01$); 1600 μg of budesonide however produced higher values at 2, 4 and from 5 to 7 hours ($p < 0.01$). In comparing the PEF values obtained with the divided dose and 400 μg budesonide it could be seen that the divided dose of budesonide had a greater effect on PEF from 7 to 12 hours ($p < 0.01$). The PEF values were significantly greater ($p < 0.05$) than initial values from the first hour onwards in the case of the highest dose of budesonide and from the second hour when the other two budesonide treatments were administered.

When the area under the curve for PEF (AUC) was calculated (TABLE 6) no significant difference could be found between the different budesonide treatments. However, when the change in area under the curve was calculated (ΔAUC) there was no difference between 1600 μg and 100 $\mu\text{g} \times 4$, but both were superior to 400 μg budesonide (TABLE 3). Both 1600 μg and 100 $\mu\text{g} \times 4$ budesonide resulted in a greater maximum increase in PEF than 400 μg budesonide (TABLE 4).

DISCUSSION

Acute dose-response studies with single doses of inhaled budesonide (Ellul-Micallef & Johansson 1983) are possible if the asthmatic patients are carefully selected. Even so, it is not uncommon for a patient who has been regarded as "stable" to suddenly undergo an increase in airflow obstruction, as happened to one of our patients. Great care must therefore be exercised in monitoring the response to a drug and the interpretation of results in this condition.

In this study an attempt has been made to determine the effects of different drug dosages (1600 µg vs 400 µg) and different dosing frequencies (400 µg vs 100 µg q.i.d.) on airflow obstruction in a group of known corticosteroid-responsive patients with chronic bronchial asthma. It would appear ideal to treat the asthmatic patient with a once daily dose of an inhaled corticosteroid in order to attain maximum patient compliance and minimize side effects. There seems to be a diurnal fluctuation in suppressibility of the hypothalamic-pituitary-adrenal axis. Hypothalamic-pituitary-adrenal function is said to be best conserved if corticosteroids are given as a single dose in the morning, mimicking the circadian rhythm, than when the dose is throughout the day. (Siegre & Klaiber 1966; Myles et al 1971.) It has been shown in normal subjects that dexamethasone given in the morning caused adrenal suppression lasting for 10 hours, whilst the same dose given at midnight resulted in a 24 hour suppression of adrenal function (Nichols et al 1965). Recent studies have shown that morning dose treatment with budesonide conserves hypothalamic-pituitary-adrenal function even when high doses were used (Toogood et al 1982). This is perhaps not surprising as budesonide is known to have a high topical anti-inflammatory and a low systemic effect (Johansson et al 1982).

The present study showed that dosing frequency had an important effect on the relief of airflow obstruction; the q.i.d. administered dose being in general the superior mode of administration from the seventh hour onwards. It has been shown that halving the frequency of inhaled budesonide keeping the same total daily dose, resulted in significant falls in PEF values (Toogood et al 1982). Similar significant falls in evening PEF values related to reductions in dosing frequencies of budesonide have also been reported. (Dahl & Johansson 1982.) Other studies report finding no differences between b.i.d. and q.i.d. administration of budesonide (Willey et al 1982; Stiksa et al 1982). Several reasons could account for these apparently conflicting results prominent amongst which is the type of patients studied and the state of their condition.

REFERENCES

- Agrup G, Björnberg Å, Elmros T, Groth O, Hannuksela H, Lassus A, Salde L, Skogh M & Thomsen K (1981). Clinical trial of a potent non-halogenated topical steroid, budesonide. *Acta Dermatovener* 61: 180-182.
- Dahl R & Johansson SÅ (1982). Clinical effect of b.i.d. and q.i.d. administration of inhaled budesonide. A double-blind controlled study. *Eur J Resp Dis* 63 (Suppl 122): 268-269.
- Ellul-Micallef R, Borthwick RC & McHardy GJR (1974). The time course of response to prednisolone in chronic bronchial asthma. *Clin Sci Mol Med* 47: 105-117.
- Ellul-Micallef R, Hansson E & Johansson SÅ (1980). Budesonide: A new corticosteroid in bronchial asthma. *Eur J Resp Dis* 61: 167-173.
- Ellul-Micallef R & Johansson SÅ (1983). Acute dose-response studies in bronchial asthma with a new corticosteroid, budesonide. *Br J Clin Pharmacol* 15: 419-422.
- Johansson SÅ, Andersson KE, Brattsand R, Gruvstad E & Hedner P (1982). Topical and systemic glucocorticoid potencies of budesonide, beclomethasone dipropionate and prednisolone in man. *Eur J Resp Dis* 63 (Suppl 122): 74-82.
- Kershner H, Klein R, Waldman D, Berger W, Rachelfsky GS, Katz R & Siegel SC (1978). Treatment of chronic childhood asthma with beclomethasone dipropionate aerosol. Effect on pituitary-adrenal function after substitution for oral corticosteroids. *Pediatrics* 62: 189-197.
- Malm L, Wihl JA, Lamm CJ & Lindqvist N (1981). Reduction of metacholine induced nasal secretion by treatment with a new topical steroid in perennial non-allergic rhinitis. *Allergy* 36: 209-214.

- Myles AB, Bacon BA & Daly JR (1971). Single daily dose corticosteroid treatment. *Ann Rheum Dis* 30: 149-153.
- Nichols T, Nugent CA & Tyler FH (1965). Diurnal variation in suppression of adrenal function by glucocorticoids. *J Clin Endocrinol* 25: 343-348.
- Ryrfeldt Å, Andersson P, Edsbäcker S, Tönnesson M, Davies D & Pauwels R (1982). Pharmacokinetics and metabolism of budesonide, a selective glucocorticoid. *Eur J Resp Dis* 63 (Suppl 122): 86-95.
- Siegre EJ & Klaiber EL (1966). Therapeutic utilisation of the diurnal variation in pituitary adrenocortical activity. *Calif Med* 104: 363-367.
- Snedecor GW & Chochran WG (1971). Statistical methods. Ames: Iowa State University Press.
- Stiksa G, Glennow C & Johannesson N (1982). An open cross-over trial with budesonide and beclomethasone dipropionate in patients with bronchial asthma. *Eur J Resp Dis* 63 (Suppl 122): 266-267.
- Toogood JH, Baskerville JC, Jennings B, Lefcoe NM & Johansson SÅ (1982). Influence of dosing frequency and schedule on the response of chronic asthmatics to the aerosol steroid, budesonide. *J Allergy Clin Immunol* 70: 288-298.
- Vaz R, Senior B, Morris M & Binkiewicz A (1982). Adrenal effects of beclomethasone inhalation therapy in asthmatic children. *J Pediatr* 100: 660-662.
- Willey RF, Godden DJ, Carmicheal J, Preston P, Frame M & Crompton G (1982). Comparison of twice daily administration of a new corticosteroid budesonide with beclomethasone dipropionate four times daily in the treatment of chronic asthma. *Br J Dis Chest* 76: 61-68.

Wyatt R, Waschek J, Weinberger M & Sherman B (1978). Effects of inhaled beclomethasone dipropionate and alternate-day prednisone on pituitary-adrenal function in children with chronic asthma. New Eng J Med 299: 1387-1392.

TABLE 1

Patient	Age	Sex	Type	FEV ₁ (ml) (predicted)	FEV ₁ (ml) (initial)	FEV ₁ (ml) (post-sal- butamol)	Eosinophils ($\times 10^6/l$)
1	38	M	Ext	3400	2050	2400	630
2	49	M	Int	3300	2200	2400	435
3	31	F	Ext	2650	1800	2100	510
4	44	M	Int	3300	1850	2400	545
5	25	F	Ext	2850	1700	2050	736
6	46	F	Ext	2200	1450	1700	394
7	23	M	Ext	4400	2500	3200	446
8	35	M	Int	3600	2650	3050	288
9	30	M	Ext	3600	2000	2450	713
10	51	F	Ext	2300	1700	1950	253
11	27	M	Ext	3400	2400	3000	475
12	40	F	Int	2600	1750	2050	537

TABLE 2

AREA UNDER CURVE (AUC)

	Placebo	Prednisolone	Budesonide		
			1600 µg	4x100 µg	400 µg
AUC	3609	4641	4594	4371	4260
S.D.	638	751	678	710	686
Difference from placebo		***	***	**	***
Difference from prednisolone			N.S.	N.S.	**
Difference from 1600 µg				N.S.	N.S.
Difference from 4x100 µg					N.S.

Area under curve, mean and standard deviation (S.D.) calculated on PEF (l/min) for placebo, prednisolone and 3 inhaled doses of budesonide (n = 11)

N.S not significant

** p < 0.01

*** p < 0.001

TABLE 3
CHANGE IN AREA UNDER CURVE (Δ AUC)

	Placebo	Prednisolone	1600 μ g	4 x 100 μ g	Budesonide 400 μ g
Δ AUC	-100	856.4	590.5	563.6	354.5
S.D.	130.1	294.7	158.7	167.6	124.9
Difference from placebo		***	***	***	***
Difference from prednisolone			*	*	***
Difference from 1600 μ g				N.S.	**
Difference from 4 x 100 μ g					**

Change in area under curve, mean and standard deviation (S.D.) calculated on PEF (l/min) for placebo, prednisolone and 3 inhaled doses of budesonide (n = 11)

N.S. not significant

* p < 0.05

** p < 0.01

*** p < 0.001

TABLE 4
MAXIMUM INCREASE IN PEF (L/MIN)

Budesonide dose (μ g)	1600	4 x 100	400
$\bar{x}$	95.5	84.5	64.5
SEM	6.5	8.1	4.7
Difference from 1600 μ g		N.S.	***
Difference from 4 x 100 μ g			*

Maximum increase in PEF (l/min), mean $\pm$ SEM for 3 inhaled doses of budesonide (n = 11)

N.S. not significant

* p < 0.05

*** p < 0.001

LEGENDS

FIGURE 1. Change in PEF (l/min), Δ PEF, Mean $\pm$ SEM after prednisolone and placebo (n = 11).

FIGURE 2. Change in PEF (l/min), Δ PEF, Mean $\pm$ SEM after 3 inhaled doses of budesonide (n = 11).

———— budesonide 1600 μ g
----- budesonide 4 x 100 μ g
..... budesonide 400 μ g

FIGURE 1

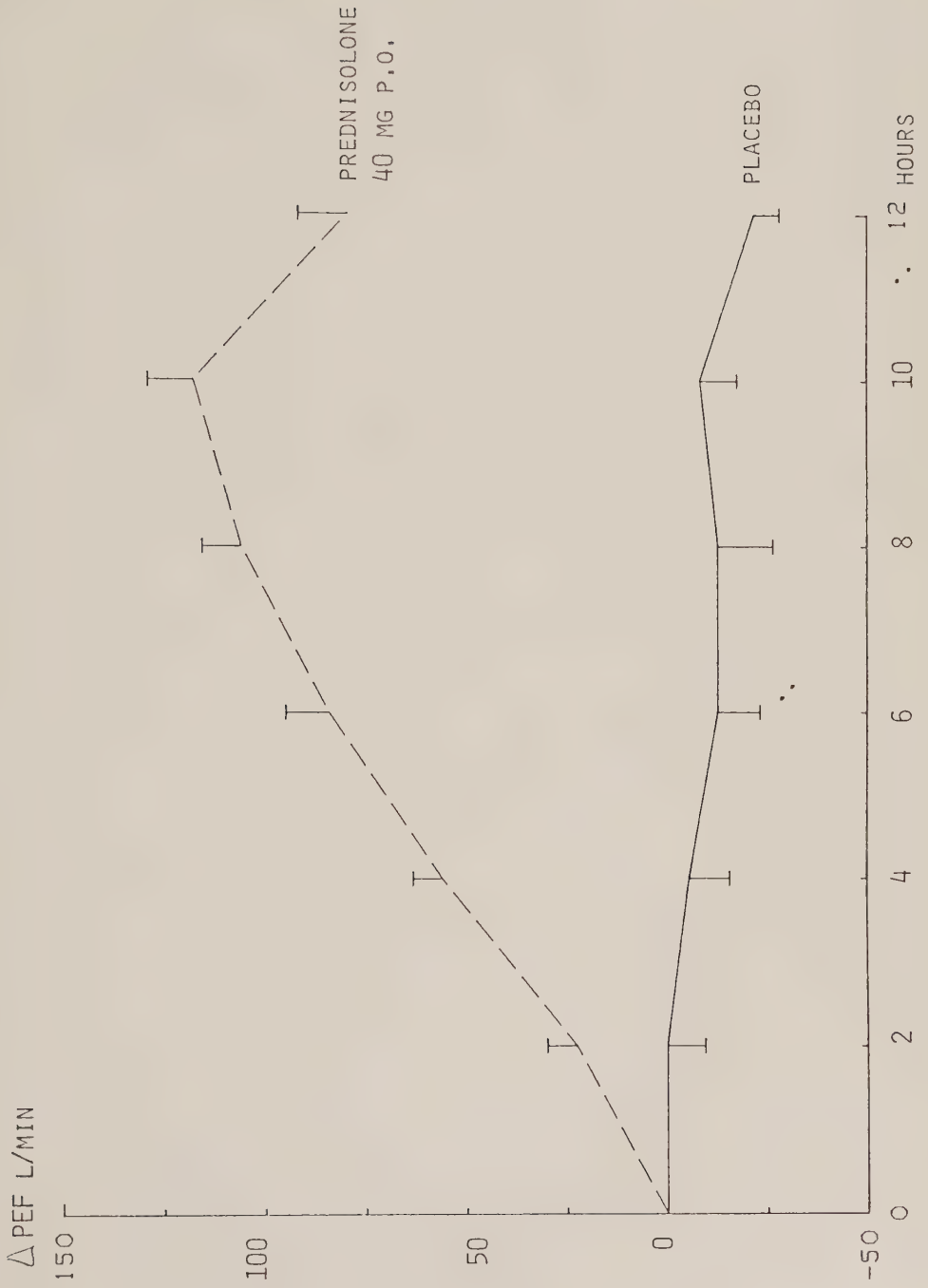
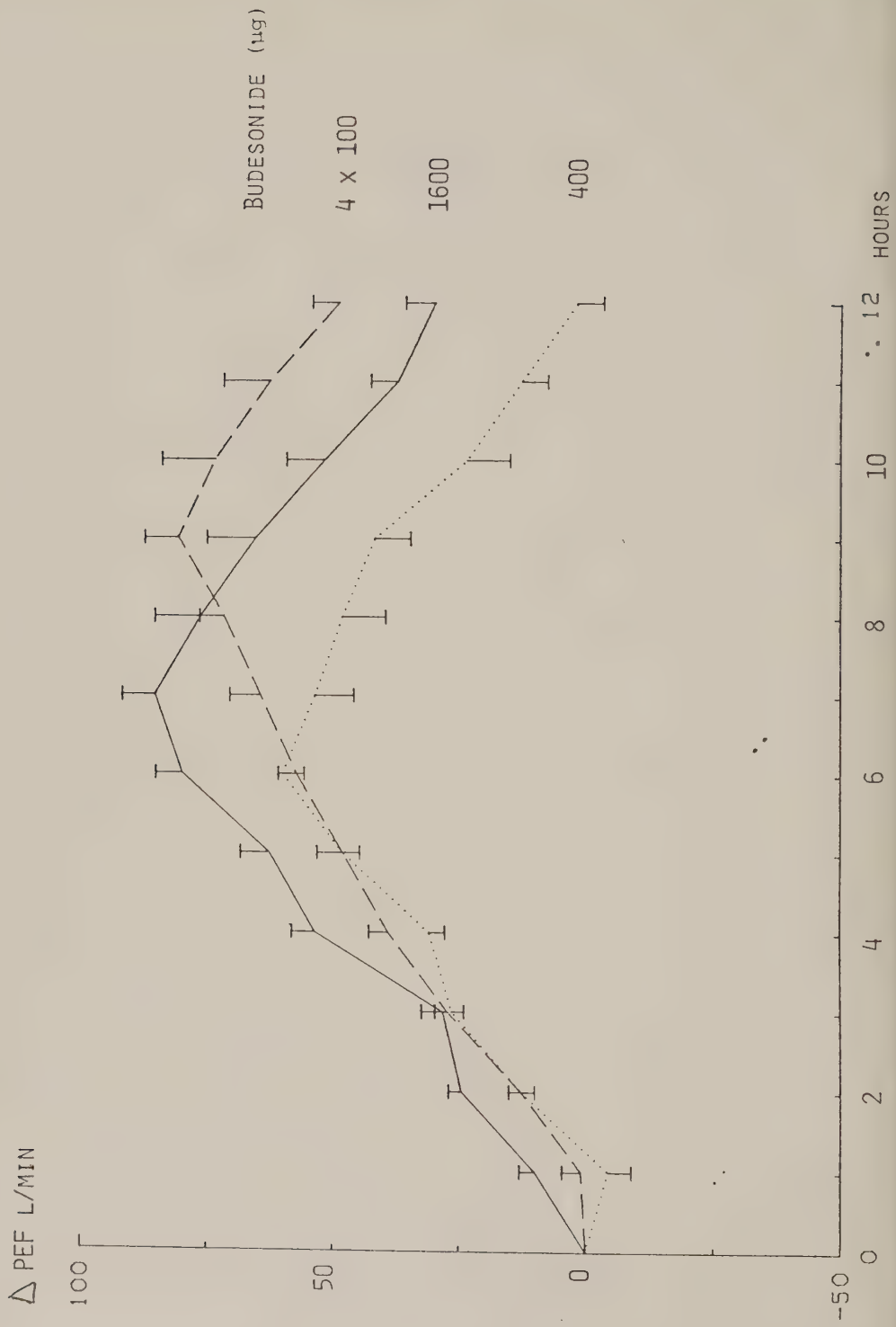


FIGURE 2



A DOUBLE-BLIND DOSE-RESPONSE STUDY OF BUDESONIDE BY INHALATION IN PATIENTS WITH BRONCHIAL ASTHMA

S-Å Johansson^{*} and R Dahl^{**}

^{*} Department for Clinical Pharmacology, University Hospital,
Lund, Sweden

^{**} Kommunehospitalet, Århus, Denmark

SUMMARY

Budesonide by inhalation and placebo were tested in 18 patients with chronic bronchial asthma of moderate degree. Three dose levels of budesonide were used (25, 100 and 400 µg q.i.d.) and the patients were to take two puffs q.i.d. in all periods. The investigation of the active treatments was performed with double-blind cross-over technique and placebo was always used at the end of the trial. The duration of each treatment period was two weeks.

The study showed a high drop-out frequency while on placebo and that the PEFR values were influenced in a dose-dependent way by budesonide. In spite of the double-blindness the patients had a tendency towards overuse of the trial aerosol on the lowest dose but they used significantly less than prescribed during the period with the highest dose. No side-effects were reported.

INTRODUCTION

During the last ten years, inhaled corticosteroids (IC) have come into wide-spread use in the treatment of asthma, gaining a reputation of being both effective and without major adverse-effects.

Although in use for nearly a decade, IC are still often used in a very standardized way and most patients on inhaled beclomethasone dipropionate (BDP) seem to be given a dose of 100 micrograms q.i.d. When needed, oral corticosteroids are given in addition to this dose of BDP. The therapeutic ratio for IC, i.e. the relation between the topical anti-inflammatory and systemic effects, is considered to be better than that for oral corticosteroids (Eriksson et al 1975, Rosenhall et al 1982, Toogood et al 1983) and although comparative dose-response studies between every morning oral corticosteroids and IC still are lacking, it would be reasonable to take advantage of the good therapeutic ratio for IC and increase the dose of inhaled steroids before the oral steroid treatment is instituted.

Although, a major step in the development of asthma treatment, BDP has in some instances given systemic effects also in the therapeutic dose range (Mygind and Hansen 1973, Toogood et al 1977, Wyatt et al 1978, Vaz et al 1982).

Budesonide is a new synthetic corticosteroid that has shown an improved therapeutic ratio in animal (Brattsand et al 1982) and man (Johansson et al 1982). Inhaled budesonide has also been shown to have an anti-asthmatic effect (Ellul-Micallef et al 1980, Björkander et al 1982, Rosenhall et al 1982, Toogood et al 1982).

The aim of the present study was to investigate the response curve for inhaled budesonide after daily doses of 100, 400 and 1600 micrograms in randomized order in patients with moderate asthma. The dose-response relationship for BDP and budesonide in patients with more pronounced asthma has been reported previously (Toogood et al 1977, Toogood et al 1982). In these studies the doses were, however, used in a non-randomized order.

MATERIAL AND METHODS

Patients -----

The study was performed in 18 adult patients suffering from bronchial asthma as defined by American College of Chest Physicians and American Thoracic Society (1975). None of the patients were sufficiently controlled by bronchodilators (β -receptor agonists and/or methylxantines) and DSCG but also needed additional medical treatment. None of the patients had chronic bronchitis or a resistive lung disease. 10 of the patients were female and 8 were male. The mean age was 46 (range 28-68) years and the mean duration of asthma was 19 (range 2-59) years. Prior to the study, 14 of the patients used inhaled BDP in a daily dose of 400 micrograms.

During the study all patients had a basal medication of β -receptor stimulants by inhalation and/or by mouth. Four patients used oral theophyllines, four used oral corticosteroids in a dose corresponding to 5-15 mg prednisolone/day. One patient used DSCG and one intranasal BDP. All drugs except inhaled β -receptor agonists were kept at fixed doses throughout the study.

The patients showed an improvement in lung function of $\geq 15\%$ within 30 minutes after two inhalations from a bronchodilator aerosol. Allergological investigations had shown an allergic component of clinical importance in eight patients to one or more of the following antigens: animal dander, house dust mite, pollens or moulds. Four patients were sensitive to aspirin and two to exercise. Eight patients had perennial rhinitis and one had urticaria.

Study design

The trial was performed as a double-blind placebo-controlled cross-over study, consisting of a run-in period of at least one week's duration, during which the patients used inhaled beclomethasone dipropionate in a daily dose of 400 micrograms (100 micrograms q.i.d.), followed by three periods each of two weeks' duration (a total of six weeks) during which the patients inhaled different doses of budesonide in randomized order.

The daily budesonide doses during the three treatment periods were 100, 400 or 1600 micrograms divided in four parts and given by a non-spacer actuator as 25, 100 and 400 micrograms q.i.d. Budesonide was inhaled from aerosols with identical formulation and appearance but with different concentrations of budesonide. The two higher doses were given with 50 microliter and the lowest with a 25 microliter valve. Two inhalations were given each time.

The study ended with a placebo period of up to two weeks' duration. The administration of placebo was to be stopped if the morning PEF during two consecutive days was $\leq 80\%$ of the mean during the run-in period. If at any other time during the study a patient deteriorated so much that he/she was at a risk of not remaining in the trial, this patient should be continued on the dose to be given in the following period.

Registration of effects

The patients registered peak expiratory flow rate (PEFR) with a mini Wright Peak Flow Meter each morning after rising, but before using any drugs. PEFR was measured again in the evening before going to bed, but after administration of the drugs for the night. Three recordings were made each time. The highest value was noted in a diary card and used for the statistical calculation.

The patients also gave their daily assessment of

- a/ breathlessness at rest
- b/ breathlessness after exertion
- c/ sleep disturbance caused by asthma
- d/ severity of asthma.

The scores were given according to a scale where 0 indicated 'well' and 10 'severe'.

Bronchodilator aerosol was used to treat acute attacks and the number of inhalations was recorded by the patients in their diary card every day.

The patients saw the investigator before the start of every new trial period and were invited to contact him at any time if feeling worse.

Candida was looked for at every visit to the hospital, and the patients were encouraged to report any side-effects by notations in their diary card.

The budesonide aerosols were returned at the end of each period and weighed for control of consumption of the drug.

Statistical method

Student's t-test for paired differences has been used and the mean of the recordings from the last four days per period or before drop-out has been used for the comparisons. The randomization was made in blocks so that each budesonide dose was equally represented during all three trial periods.

Ethical aspects

The study was performed in accordance with "the Declaration of Helsinki" and informed consent was obtained from all participants before the onset of the trial. The study was approved by the Danish health authorities.

RESULTS

18 patients participated in the trial. However, in the placebo period PEFR is calculated in 16 patients as two patients dropped out during the third period with budesonide. Both patients used the lowest dose of budesonide (25 micrograms q.i.d.) in this period, and they are both included in the analysis of this dose level. The number of patients as a function of time in the trial is shown in FIG 1.

The number of patients for whom scores are given is lower because some patients did not give subjective scores for all parameters.

Use of trial aerosols

The prescribed dose was in all periods 8 inhalations/day. During the period with 100 micrograms q.i.d. (middle dose) the observed use and expected use were almost identical. In the period with the lowest dose there was a non-significant tendency to increase the daily number of inhalations and when on the highest dose there was a statistically significant difference between the real use and the prescribed use. The use during the high dose period was also lower than during both other periods. TABLE 1.

Peak expiratory flow rate (PEFR)

A dose-dependent variation in PEFR was found both in the morning and in the evening. TABLE 2, FIG 2. When comparing the morning PEFR values, only the values after the highest dose of budesonide were significantly different from placebo but in the evening also the middle dose and placebo were significantly different.

Subjective evaluation

The patients' symptom scores for breathlessness at rest and at exertion showed that the two highest doses of budesonide were superior to placebo and the lowest dose of budesonide. TABLE 3.

Concerning the patients' evaluation of sleep disturbances caused by asthma, budesonide 400 and 1600 micrograms per day were superior to placebo, and 400 micrograms daily was also superior to 100 micrograms. TABLE 3.

The score for asthma severity showed that budesonide 400 and 1600 micrograms per day were superior to 100 micrograms daily, but only a daily dose of 400 micrograms budesonide was statistically different from placebo. TABLE 3.

When calculating the number of inhalations from bronchodilator aerosols during the trial, only budesonide 400 micrograms/day had a significantly lower value than placebo. TABLE 3.

Candidiasis and hoarseness were not reported during the study.

DISCUSSION

There was a high drop-out rate during the placebo period. FIG 1. This strongly indicates that all dose-levels tested were more effective than placebo, but it also created a problem - either those patients who dropped out had to be omitted from the statistical analysis between placebo and the active treatments or had to be included using a value obtained before they dropped out. If the first choice was made it would, in the extreme, result in comparing a treatment with placebo in patients who were so stable in their asthma that they could tolerate the substitution of corticosteroids with placebo for at least two weeks, or perhaps they were in no present need of the investigated treatment at all. Whatever the reason, this choice would probably overestimate the relative effect of placebo as an alternative treatment for inhaled corticosteroids.

If, on the other hand, the patients who dropped out remained in the statistical comparison with the value obtained before they dropped out, this could also result in an overestimation of the effect of placebo as the measured values would to a great extent be residual effects from the last, preceding active treatment period. Although far from ideal, we found this second alternative better and decided to include all patients in the statistical analysis in treatment periods in which they had participated for at least four days. For comparison between treatments we used the mean of the last four days per treatment period for each individual or the mean of the last four days before a patient dropped

out. The last four days of a two weeks period were used as it has been reported previously that when treated for two weeks the effect-plateau was usually reached within ten days. (Björkander et al 1982.) The mean of the last four days was used as this substantially reduced the standard deviation compared to when the last day or the mean of the last two or three days were used.

The deviation from the prescribed dose caused some problems in evaluating the results. All trial aerosols had the same appearance and the composition of the contents was identical except for the concentration of budesonide. The lowest dose was given by a 25 microliter valve and the two other with a 50 microliter valve. Budesonide itself has very little, if any, taste. We therefore regard the changes in dose as a reflexion of an improvement in the asthmatic condition although this was not exactly paralleled in the subjective evaluation where better values were sometimes given for 400 than for 1600 micrograms/day although there was no significant difference between them. Scores were on the other hand not given by all patients and therefore the PEF recordings may be regarded as the most accurate measure for therapeutic effect.

The patients in this study showed a dose-dependent anti-asthmatic effect of inhaled budesonide and already the lowest dose gave some protection. These results are in conformity with those from the non-prednisone users in a study by Toogood et al (1982), whereas the prednisone users in the same study needed a higher dose to obtain the same improvement in lung function. A direct

comparison between the two studies is hard to make because of the difference in method but in spite of the differences, the similarity in results is striking and both studies clearly demonstrate that the dose of inhaled budesonide should be individualized to give optimum benefit to the patients.

REFERENCES

1. American College of Chest Physicians and American Thoracic Society: Pulmonary terms and symbols. A report of the ACCP ATS Joint Committee on Pulmonary Nomenclature. Chest 67, 583-593, 1975.
2. Björkander J, Formgren H, Johansson SÅ, Millqvist E: Methodological aspects on clinical trials with inhaled corticosteroids: Results of two comparisons between two steroid aerosols in patients with asthma. Eur J Resp Dis Suppl 122, 63, 108-117, 1982.
3. Brattsand R, Thalén A, Roempke K, Källström L, Gruvstad E: Development of new glucocorticosteroids with a very high ratio between topical and systemic activities. Eur J Resp Dis Suppl 122, 63, 62-73, 1982.
4. Ellul-Micallef R, Hansson E, Johansson SÅ: Budesonide: A new corticosteroid in bronchial asthma. Eur J Resp Dis 61, 167-173, 1980.
5. Eriksson NE, Lindgren S, Lindholm N: A double-blind comparison of beclomethasone dipropionate aerosol and prednisolone in asthmatic patients. Postgrad Med J 51 (Suppl 4), '67-70, 1975.
6. Johansson SÅ, Andersson KE, Brattsand R, Gruvstad E, Hedner P: Topical and systemic glucocorticoid potencies of budesonide and beclomethasone dipropionate in man. Eur J Clin Pharmacol 22, 523-529, 1982.

7. Mygind N, Hansen J: Beclomethasone dipropionate aerosol effect on the adrenals in normal persons. *Acta Allergy* 28, 211-218, 1973.
8. Rosenhall L, Lundqvist G, Adeloeth E, Glennow C: Comparison between inhaled and oral corticosteroids in patients with chronic asthma. *Eur J Resp Dis Suppl* 122, 63, 154-162, 1982.
9. Toogood JH, Baskerville JC, Jennings B, Lefcoe NM, Johansson SA: Influence of dosing frequency and schedule on the response of chronic asthmatics to the aerosol steroid, budesonide. *J Allergy Clin Immunol* 70, 4, 288-298, 1982.
10. Toogood JH, Lefcoe NH, Haines DSM, Jennings B, Errington M, Baksh L, Chuang L: A graded dose assessment of the efficacy of beclomethasone dipropionate aerosol for severe chronic asthma. *J Allergy* 59, 298-308, 1977.
11. Vaz R, Senior B, Morris M, Binkiewicz A: Adrenal effect of beclomethasone inhalation therapy in asthmatic children. *J Pediatr* 100, 4, 660-662, 1982.
12. Wyatt R, Wascheck J, Weinberger M, Sherman B: Effect of inhaled beclomethasone dipropionate and alternate day prednisone on pituitary adrenal function in children with chronic asthma. *New Engl J Med* 299, 1387-1392, 1978.

FIG 1

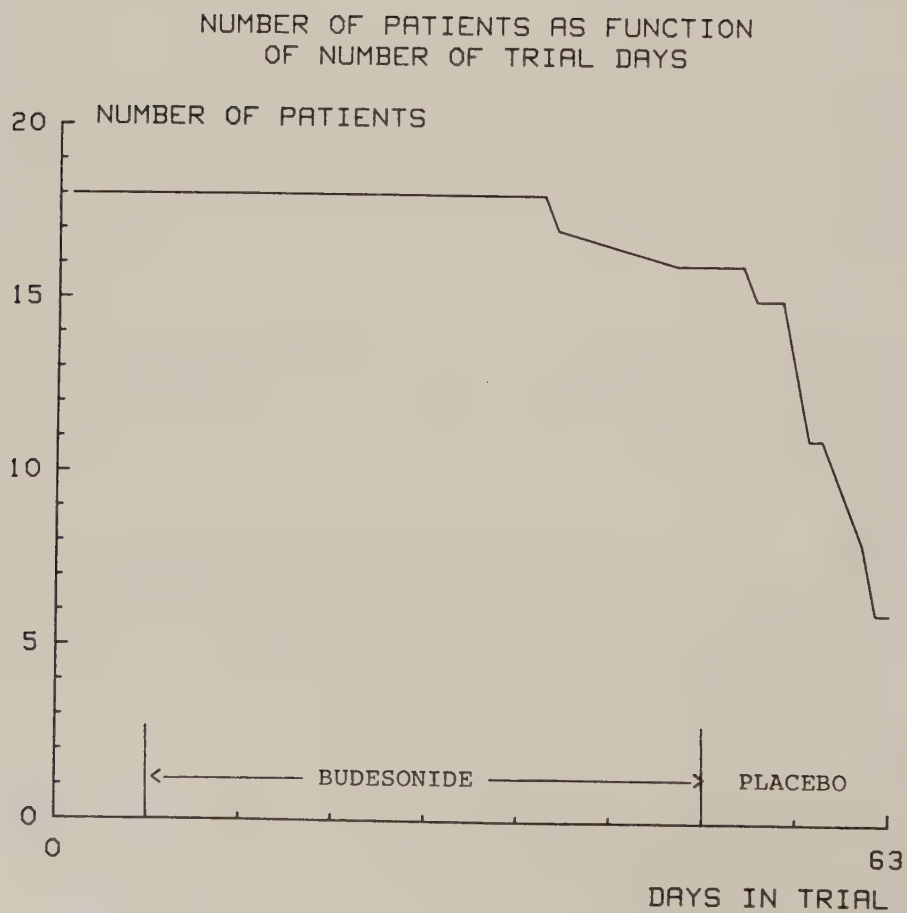


FIG 2

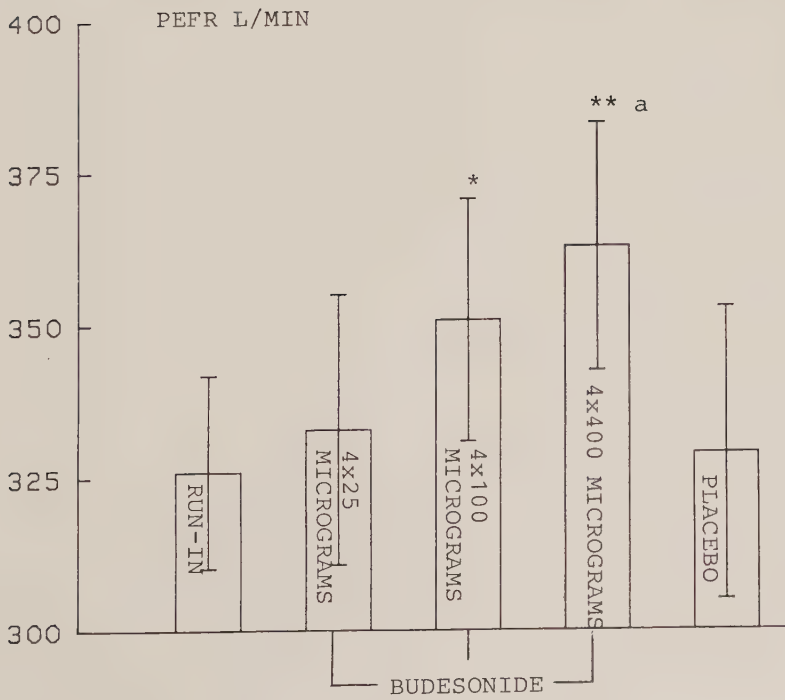


TABLE 1

	100 micrograms/day		400 micrograms/day		1600 micrograms/day	
	Number of inhalations	Dose micro- gram	Number of inhalations	Dose micro- gram	Number of inhalations	Dose micro- gram
$\bar{X}$	8.71 ^a	109	7.99 ^a	395	5.89 ^{***}	1178
SEM	0.99	12	0.67	34	0.42	84

*** p < 0.001 Difference vs intended no of inhalations

^a p < 0.05 Difference vs 1600 microgram/day

TABLE 2

Drug/dose microgram	M ± SEM
Run-in	306 ± 19
Budesonide 25 q.i.d.	300 ± 27
Budesonide 100 q.i.d.	319 ± 23
	*aa
Budesonide 400 q.i.d.	334 ± 23
Placebo 0 q.i.d.	308 ± 30

* p < 0.05 Difference vs Placebo

aa p < 0.01 Difference vs Bud 25 microgram q.i.d.

TABLE 3

Subjective evaluation (M $\pm$ SEM)

	Budesonide microgram/day				
	Run-in	100	400	1600	Placebo
Breathlessness			a **	a *	
at rest	1.56 $\pm$ 0.32	1.89 $\pm$ 0.42	0.94 $\pm$ 0.3	1.27 $\pm$ 0.33	2.37 $\pm$ 0.63
			a *	aaa *	
at exertion	2.70 $\pm$ 0.49	2.83 $\pm$ 0.39	1.71 $\pm$ 0.43	1.98 $\pm$ 0.42	3.06 $\pm$ 0.68
Sleep			a **	*	
disturbances	1.59 $\pm$ 0.26	2.18 $\pm$ 0.48	1.27 $\pm$ 0.33	1.41 $\pm$ 0.40	2.98 $\pm$ 0.78
caused by asthma					
Asthma			a ***	aa	
severity score	2.73 $\pm$ 0.41	3.03 $\pm$ 0.38	1.8 $\pm$ 0.40	2.25 $\pm$ 0.41	3.41 $\pm$ 0.62
Daily number of extra bronchodil inhalations	3.61 $\pm$ 0.56	3.82 $\pm$ 0.76	2.74 $\pm$ 0.61	2.44 $\pm$ 0.68	5.31 $\pm$ 0.83

* p < 0.05

** p < 0.01

*** p < 0.001

Difference versus placebo

a p < 0.05

aa p < 0.01

aaa p < 0.001

Difference versus budesonide

100 microgram (25 microgram q.i.d.)

LEGENDS TO FIGURES

FIG 1. The number of patients as a function of treatment-time. The decrease during the last part of the budesonide period was due to drop-out of two patients on 25 μg q.i.d.

FIG 2. PEFR (l/min) in the evening in the different treatment periods ($M \pm \text{SEM}$, $n = 18$).

*	$p < 0.05$	}	Difference vs placebo
**	$p < 0.01$		
a	$p < 0.05$		Difference vs budesonide 25 μg q.i.d.

LEGENDS TO TABLES

TABLE 1. Mean daily number of inhalations of budesonide and real dose at the different intended dose-levels.

*** $p < 0.001$ Difference vs intended number of inhalations

a $p < 0.05$ Difference vs "1600 μg "/day

TABLE 2. PEFR (l/min) in the morning in the different treatment periods ($M \pm \text{SEM}$, $n = 18$).

* $p < 0.05$ Difference vs placebo

aa $p < 0.01$ Difference vs budesonide 25 μg q.i.d.

TABLE 3. The patients' rating of the asthma during the different treatments. ($M \pm \text{SEM}$, $n =$).

* $p < 0.05$ ** $p < 0.01$ *** $p < 0.001$	}	Difference vs placebo
---	---	-----------------------

a $p < 0.05$ aa $p < 0.01$ aaa $p < 0.001$	}	Difference vs budesonide 25 μg q.i.d.
---	---	--

VII

Influence of dosing frequency and schedule on the response of chronic asthmatics to the aerosol steroid, budesonide

J. H. Toogood, M.D., F.R.C.P.(C), J. C. Baskerville, Ph.D.,*
Barbara Jennings, B.A., N. M. Lefcoe, M.D., F.R.C.P.(C), and
S. A. Johansson, M.Ph.Sci.** London, Ontario, Canada

The influence of various dosing regimens on the response of asthmatic patients to aerosol steroid was investigated. Budesonide, a topically active corticosteroid like beclomethasone dipropionate, was given q.i.d. or b.i.d., in the morning or A.M./P.M., at doses of 400, 800, and 1600 µg/day. Each patient (n = 34) took every treatment combination for 2 wk. The antiasthmatic and systemic effects, measured by changes in peak expiratory flow rate (PEFR), blood eosinophils, and serum cortisol levels increased approximately linearly on log dose budesonide ($p < 0.0005$). Systemic effects of the drug were nonsignificant at low dosage. At high dosage, morning dosing conserved hypothalamic-pituitary-adrenal function, but at the cost of a marginal reduction in efficacy (Δ PEFR, $p = 0.12$). Halving the dose frequency reduced the antiasthmatic potency of the drug, i.e., PEFR fell by an amount equivalent to approximately eightfold reduction in daily dosage ($p = 0.002$). This effect was not evident when asthma was in remission but became so with asthma in relapse. Overall, the q.i.d. A.M./P.M. regimen showed the best risk-benefit relationships. The data indicate (1) that reductions in dose frequency made with the hope of improving patient compliance and thus conserving the drug's long-term efficacy are likely to lead to the reverse effect, (2) that the clinician can conserve a better balance of risk vs benefit by titrating dosage in terms of puffs per dose rather than doses per day, and (3) that patients can increase the antiasthmatic efficacy of this aerosol steroid without any increase in drug costs (or apparent risk) by simply increasing dosing frequency. These therapeutic considerations probably apply to some or all of the other topically active steroids currently used to treat asthma. (J ALLERGY CLIN IMMUNOL 70:288, 1982.)

Although the usefulness of topically active steroid aerosols for asthma is well established,¹⁻¹¹ the influence of the dosing regimen on the efficacy and safety of this class of drugs has not been studied in detail. The importance of such studies has been emphasized.¹² It would seem reasonable that any reduction from the conventional q.i.d. dose frequency should help to improve patient compliance, and in practice, patients often do this with or without the

sanction of their physician. Less frequent dosing has been advocated recently to improve the long-term

Abbreviations used:

ADS:	Asthma disability score
ANCOVA:	Analysis of covariance
ANOVA:	Analysis of variance
BDP:	Beclomethasone dipropionate
BL1:	Baseline 1
BL2:	Baseline 2
CISP:	Clinical illness score (scored by patient)
EOS:	Total blood eosinophil count
FEV ₁ :	Forced expiratory volume in one second
HPA:	Hypothalamic-pituitary-adrenal
MLPF:	Seven-day mean of the lower of two peak flows measured daily during the second week of each treatment period
PEFR:	Peak expiratory flow rate
SC:	Serum cortisol

From the Victoria Hospital Department of Medicine and the University of Western Ontario Medical School, London, Ontario, Canada.

Supported by a grant from Ab Draco, Lund, Sweden.

Received for publication March 17, 1982.

Accepted for publication May 24, 1982.

Reprint requests to: J. H. Toogood, M.D., F.R.C.P.(C), Allergy Clinic, Victoria Hospital, 375 South St., London, Ontario, Canada N6A 4G5.

*Baskerville Associates, London, Ontario.

**AB Draco, Lund, Sweden.

TABLE I. Patient characteristics before BL1*

	n		Mean	SE	
Male	21	Age (yr)	54.9	1.9	
Female	13	Years of asthma	21.0	2.3	
Asthma	34	FVC	91.1	3.1	
Recurrent mucopurulent bronchitis	16	FEV ₁	62.6	3.9	
Chronic bronchitis		% PN			
Yes	12		FEF ₂₅₋₇₅	29.8	2.5
No	22		DLCO _{ss}	102.2	6.2
Bronchodilator inhalant used	27	Asthma frequency	5.6	0.8	
Smokers		(days/2 wk)	5.6	0.8	
Current	1	Inhaler usage (doses/2 wk)	29.8	5.3	
Ex-	8	Blood eosinophils/mm ³	546.0	56.0	
Never	25	Serum IgE	358.0	130.0	
		Positive skin tests (%)	42.9	4.9	
Perennial or seasonal rhinitis	12	A.M. SC (μg/dl)	11.8	1.0	
Polyps or hyperplastic sinusitis	22				
Prednisone-dependent	19	Prednisone (n = 19)	8.4	1.9	
		(mg/day)			
Beclomethasone user	34	Beclomethasone (n = 34)	0.4	0.0	
		(mg/day)			

Prednisone-dependent		No prednisone		t value	p value	
Mean	SE	Mean	SE			
FEV ₁ (L/sec)	1.5	0.13	2.2	0.20	-2.63	0.02
Blood eosinophils/mm ³	660.0	79.6	401.0	63.3	2.44	0.02
A.M. SC (μg/dl)	10.0	1.5	14.1	1.0	-2.05	0.05

FVC = forced vital capacity; FEF₂₅₋₇₅ = forced expiratory flow at 25% to 75% FVC; DLCO_{ss} = steady-state pulmonary diffusing capacity; PN = predicted normal.

*Bronchitis was diagnosed by conventional questionnaire criteria.⁴⁰ Skin-test reactivity was rated by the number of positive reactions with a set of 20 common allergens tested intradermally in every subject. The 19 prednisone-dependent patients had significantly more eosinophilia and airflow reduction (FEV₁) and lower A.M. SC levels than the 15 patients who did not use oral prednisone.

efficacy of BDP treatment.¹³ In addition, if the entire daily dose could be administered in the morning, this should conserve HPA function to some extent, as it does with oral prednisone,¹⁴ and it might thus facilitate the use of larger doses. Some asthmatics need larger doses of aerosol steroid than others to achieve equivalent levels of clinical or functional response, yet the larger doses suppress HPA function.^{2, 5, 7, 15, 16}

We assessed the influence of the dosing regimen on the results of aerosol steroid treatment by systematically varying the dose per day, the dose frequency, and the dosing schedule (A.M. vs. A.M./P.M.) during a trial of treatment with budesonide, a topically active corticosteroid that is available in formulations that deliver either 50 or 200 μg per aerosol puff. The study confirmed that morning-dose treatment does in fact conserve HPA function when high doses of aerosol steroid are used, but at the cost of a slight reduction in efficacy. Dose frequency was found to exert an important effect on the treatment response.

METHODS

The study group comprised 34 adult outpatients with chronic asthma conforming to conventional diagnostic criteria,^{17, 18} who had benefited previously from BDP treatment and who had morning SC levels ≥ 7 μg/dl. Nineteen regularly used oral prednisone on alternate mornings; 15 did not use prednisone. These and other relevant patient characteristics are summarized in Table I. The treatment drug, budesonide (AB Draco, Lund, subsidiary of AB Astra, Sweden), is a nonhalogenated corticosteroid¹⁹ with high topical anti-inflammatory potency²⁰ and low bioavailability²¹ that is not metabolized in the lung²¹ and produces less systemic effect than BDP after absorption.²⁰ Each puff from the pressurized canister delivers either 50 or 200 μg of budesonide plus 69.9 mg of Freon propellants and sorbitan trioleate.

The study design was a balanced crossover, comparing two dose frequencies (b.i.d. or q.i.d.) at three levels of budesonide dosage (400, 800, and 1600 μg/day) given by two dosing schedules (A.M. or A.M./P.M.). Every patient received each treatment combination for 2 wk. The four combinations of dosing frequency and dose scheduling,

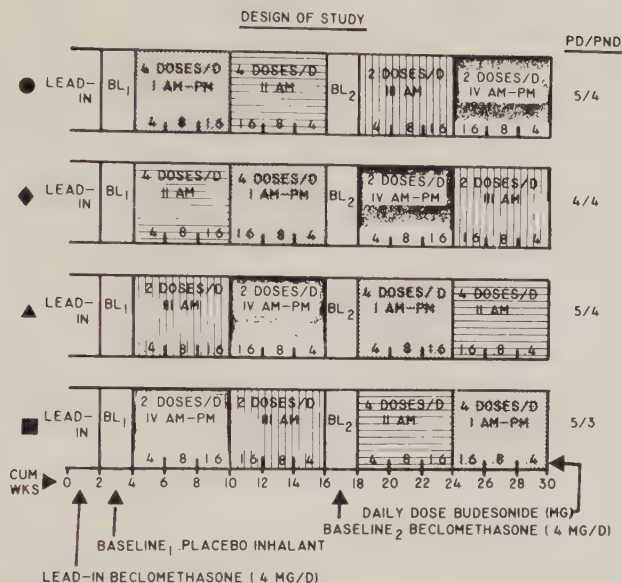


FIG. 1. The protocol was designed to assess the effects of daily dose, dose frequency, and dose scheduling on the response of asthmatics to budesonide aerosol. Prednisone dependent (PD, $n = 19$) and nondependent (PND, $n = 15$) patients shown by the figures on the right were randomized among the four treatment combinations (I, II, III, IV) to create the patient subgroups identified by the symbols on the left. Budesonide dosage/day (0.4, 0.8, and 1.6 mg) and scheduling (A.M. or A.M./P.M.) were balanced within each half of the study. Dose frequency (b.i.d. or q.i.d.) was crossed over at BL2. BL1 and BL2 treatments differed for reasons explained in the text. Lead-in data were not included in the ANOVA.

identified by the Roman numerals I to IV, were balanced across the four treatment sequences as shown in Fig. 1. Prednisone users and nonusers were separately randomized to these treatment sequences. The two baseline periods (BL1 and BL2) are shown in the Fig. 1, and our original plan was to use a placebo inhalant, single blind, during each. However, because the study coincided with the allergenic pollen seasons in this region and some severe asthma relapses occurred during BL1, it was deemed unethical to proceed with the use of a placebo in BL2. The single-blind feature was retained, but BDP 400 $\mu\text{g}/\text{day}$ was given instead. Budesonide treatment responses for the first and second halves of the study were measured by changes from BL1 and BL2, respectively, and analyzed by ANOVA. Because frequency crossed over only at BL2 it was necessary to compare the data to BL2 as well as BL1. The inclusion of the BL2 data in ANOVA has no numerical effect on the comparisons between doses or between schedules, since those were balanced equally within both halves of the study (Fig. 1). The differences between means at each dose level and baseline were also individually tested with estimates of standard errors derived from the appropriate error terms in ANOVA.

PEFRs were recorded twice daily at home, and the MLPF was analyzed. Spirometric measurements were performed in the clinic at the end of every 2 wk period. At these visits the physician used a standardized validated scale to deter-

mine the ADS.²² Independently, each patient rated his or her clinical illness severity (CISP) using the same questionnaire²² expanded to a 26 point scale to improve discriminating power at the lower (nondisabled) end of the scale. Furthermore, at these visits, diary records of all medications used, including prednisone, were checked against pill counts, and blood was drawn at 0800 hr for EOS and SC level (24 hr after the last prednisone dose, if oral steroid was in use). Prednisone use was strictly controlled by one physician. Bronchodilators and aerosol steroid were omitted after 2200 hr the day before the clinic visit. Cortisol assays were performed en bloc after completion of the study, using the competitive protein-binding method of Murphy.²³

The mode of inhalation of the budesonide or BDP conformed with the package insert instructions for BDP and was the same throughout the study. The q.i.d. A.M./P.M. budesonide doses were scheduled at 0800, 1200, 1730, and 2200 hr; b.i.d. A.M./P.M. doses were given at 0800 and 2200 hr; A.M. doses ($\times 2$) were given at 0800 and 1200 hr; and A.M. doses ($\times 4$) were given at 0700, 0900, 1030, and 1200 hr. During BL1 and BL2 the placebo or BDP was given q.i.d., A.M./P.M. The budesonide canisters were weighed before and after each visit, and the difference between observed and prescribed changes in canister weights was used as a measure of each patient's compliance with the stipulated budesonide dosage.

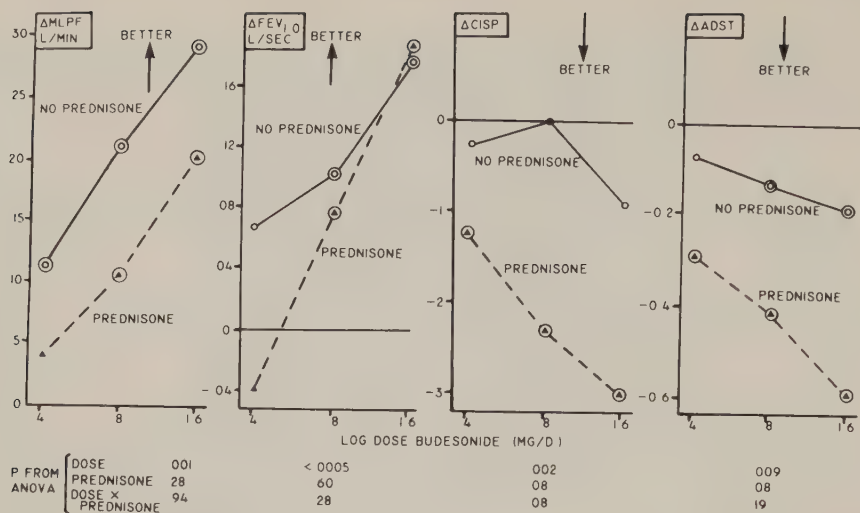


FIG. 2. Efficacy of graduated doses of budesonide is illustrated. Each point represents the group mean (four observations per patient). Responses of 19 prednisone-dependent and 15 nondependent patients are shown separately. Every patient took each treatment combination. Circled points differ significantly from the prebudesonide baseline ($p \leq 0.05$). Relevant p values from ANOVA are shown at the bottom.

RESULTS

Compliance with the prescribed budesonide usage averaged 97.4% throughout the study (range 78% to 155%). The budesonide treatment produced significant dose-dependent improvement in the four asthma response indices shown in Fig. 2: airflows measured daily (ΔMLPF , $p = 0.001$) and every 2 wk (ΔFEV_1 , $p < 0.0005$), the patients' rating of symptom severity (ΔCISP , $p = 0.002$), and the physician's rating of asthma disability (ΔADS , $p = 0.009$). Symptoms (CISP) and disability ratings (ADS) but not airflows (MLPF or FEV_1) improved more in the prednisone users. Since the standard deviations were large, these differences between prednisone users and nonusers were not statistically significant (see p values from ANOVA, Fig. 2).

A dose-dependent suppression occurred in blood eosinophils ($p < 0.0005$) and A.M. SC levels ($p < 0.0005$) (Fig. 3). In the prednisone users this was statistically significant at doses of 800 and 1600 μg budesonide/day ($p \leq 0.05$). In patients not using prednisone, the change from baseline was significant only at 1600 μg budesonide/day. All these changes, reflecting the local effect of the drug in the lung and its indirect (i.e., HPA mediated) or direct effects on other systems after absorption, were approximately linear on log dose (Figs. 2 and 3).

Because of the asthma relapses during and immediately after BL1, prednisone usage was not equally

balanced across all budesonide treatment and baseline periods. For example, in the 400, 800, and 1600 μg dose periods, the patients averaged 0.01, 0.29, and 1.24 mg/day, respectively, less prednisone than during baseline time. Therefore we investigated the possibility that this imbalance might have affected the responses to budesonide by using the pill-count records of prednisone usage as a covariate in an ANCOVA. Prednisone usage did not show a significant relationship to any budesonide treatment response, i.e., to the effects of the dose, frequency, or scheduling of budesonide on ΔMLPF , ΔFEV_1 , ΔEOS , or ΔSC ($p > 0.05$, ANCOVA). Therefore these additional data from the ANCOVA are not shown in detail here.

The effects of shifting the entire budesonide dose to before noon are illustrated in Fig. 4. Morning dosing did not affect the eosinophil response to budesonide ($p = 0.17$), but it did alter HPA responsiveness, as shown by the A.M. SC level. There was a significant interaction between the daily dose and the dosing schedule ($p = 0.03$), such that the shift to morning dosing tended to conserve endogenous cortisol secretion at high budesonide dosage ($> 800 \mu\text{g/day}$). There was no conclusive evidence that this HPA-sparing effect was greater in patients using both budesonide and prednisone than in those receiving budesonide alone (dose $\times$ prednisone $\times$ periodicity interaction, $p = 0.10$ by ANOVA). Morning dosing reduced the antiasthmatic potency of budesonide, as

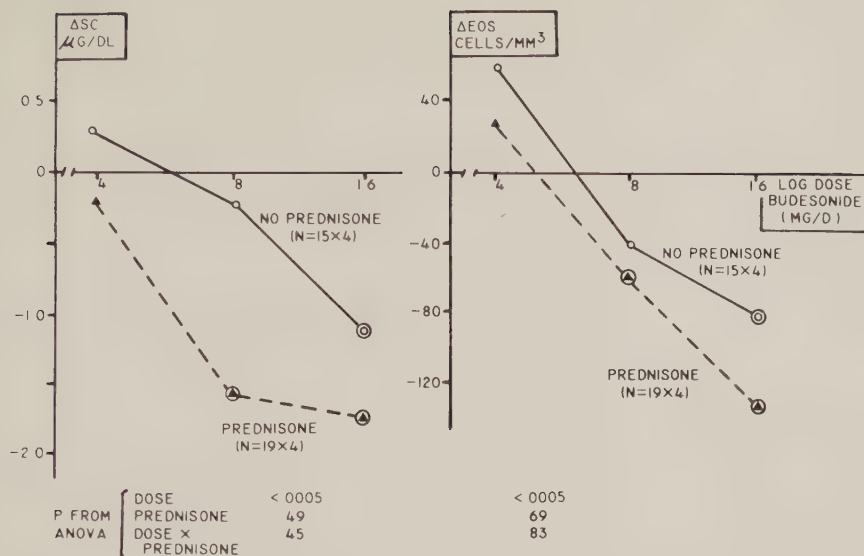


FIG. 3. Changes in EOS and 0800 hr SC levels are plotted against log dose budesonide. Each point represents the group mean (four observations per patient). Responses of prednisone-dependent and nondependent patients are shown separately. Circled points differ significantly from baseline ($p \leq 0.05$). The p values from ANOVA show a significant effect of budesonide daily dosage but no significant additive effect or synergistic interaction from concomitant prednisone usage.

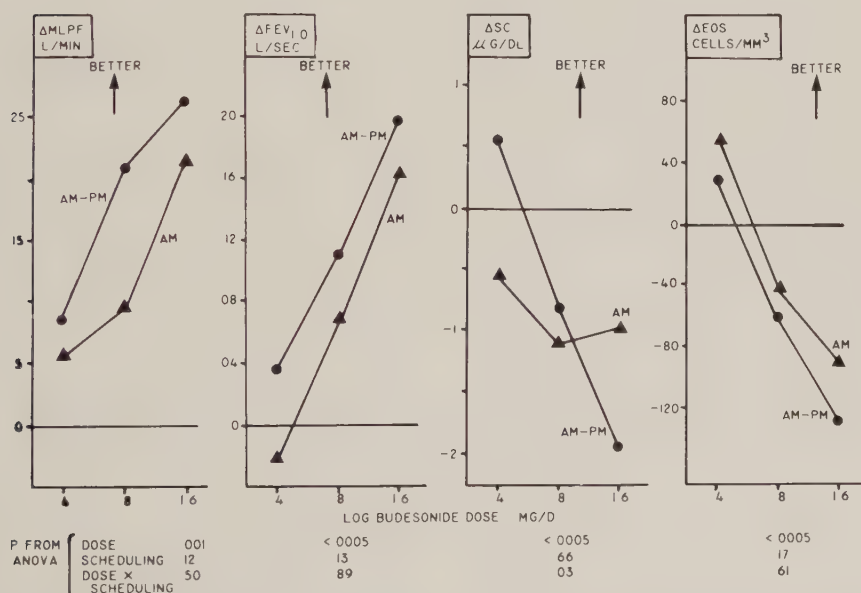


FIG. 4. Effects of A.M. vs A.M./P.M. dosing regimens on airflows and systemic absorption indices are compared over a range of budesonide doses. Each point represents the group mean (two observations per patient). The p values derived from ANOVA quantify the significance of the effects of daily dose, dose scheduling, and dose-scheduling interactions for each index shown.

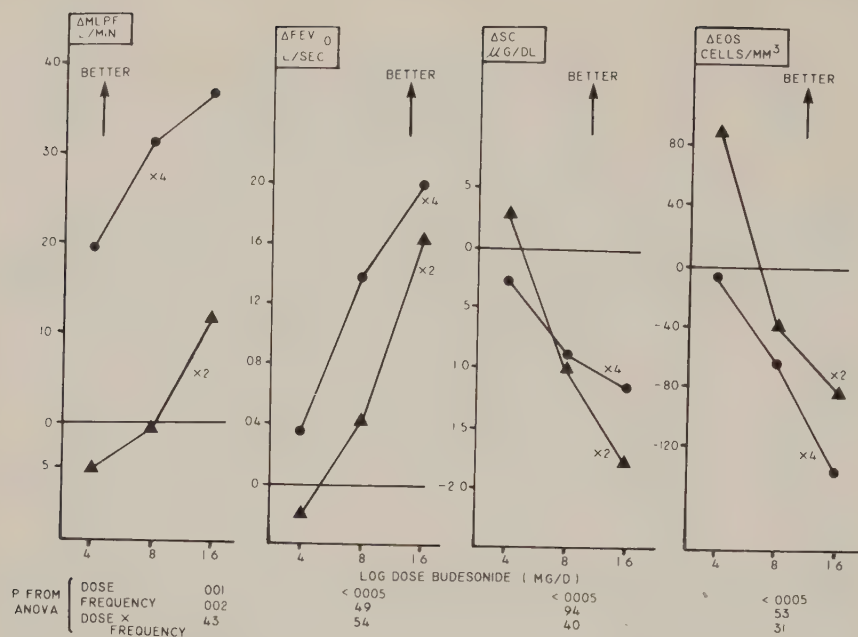


FIG. 5. Effects of b.i.d. vs q.i.d. dosing frequencies on indices of airway response and systemic steroid absorption are compared over a range of budesonide doses. Each point represents the group mean (two observations per patient). The p values from ANOVA quantify the significance for each response index of the influence of daily dose, dose frequency, and of dose-frequency interactions.

illustrated by the airflow indices shown in Fig. 4. The reduction was not statistically significant but was consistent for all four asthma response indices. The effect of morning dosing on Δ MLPF showed the strongest evidence of a difference by ANOVA ($p = 0.12$, Fig. 4), and the drop in peak flows was equivalent to a reduction in daily dose of approximately 40%.

The effects of dose frequency on the A.M. SC levels and blood eosinophils were nonsignificant (Fig. 5). However, the shift from q.i.d. to b.i.d. dosing was associated with a loss of efficacy equivalent to about an 80% reduction in the daily dose of the drug, as measured by the daily peak flows ($p = 0.002$). Parallel but nonsignificant changes occurred in Δ FEV₁ ($p = 0.49$) and Δ CISP ($p = 0.09$). The significant effect of dose frequency on Δ MLPF was mostly due to data from the first half of the study referenced to BL1 (placebo treated, Fig. 6). Asthma was worse during BL1, as measured by paired t tests of the group means: MLPF ($p = 0.002$), FEV₁ ($p = 0.007$), CISP ($p < 0.0005$), and ADS ($p < 0.0005$).

The relationship between the local and the systemic responses to budesonide as functions of increasing drug dosage is illustrated in Fig. 7. This provides a basis for comparing risk with benefit in bioequivalent terms.

DISCUSSION

Effects of budesonide

The antiasthmatic activity of budesonide in these patients is in accord with the results of several other clinical studies.^{24, 25} The log dose-response characteristics of both the local (antiasthmatic) and systemic effects of the drug closely resemble those previously demonstrated for BDP.^{7, 15} The accompanying changes in SC (Figs. 3 and 5) suggest that the dose-dependent eosinopenic response reflects mainly the systemic action of the drug, although it is possible that some of the change accrues from its anti-inflammatory action in the lungs. The imbalance between the two baselines with respect to asthma control (which reflects the difference in treatments, placebo vs. BDP) results in an underestimate of the antiasthmatic potency of budesonide in this study. Thus these data should be viewed as a conservative estimate of the drug's efficacy in contrast to that expected if it were compared with placebo alone. The estimates of systemic potency are not similarly affected, since there was no imbalance of EOS or SC between the baselines. In this study, budesonide appeared at least as potent as BDP, but the design of the study does not permit a precise estimate of the relative potency of the two drugs, either in terms of their antiasthmatic or

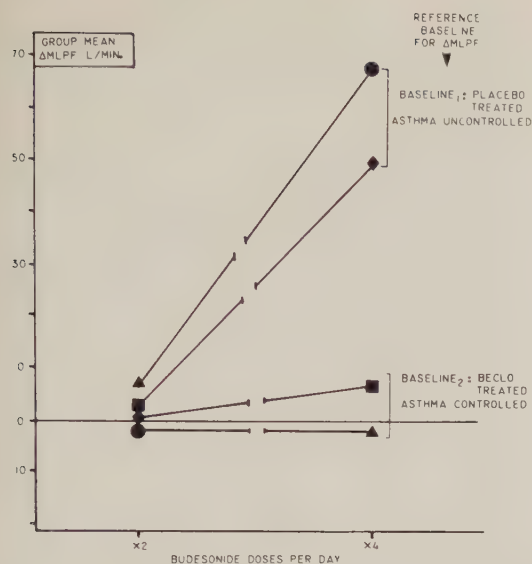


FIG. 6. In these patients, asthma was poorly controlled during BL1 (on placebo) and better controlled in BL2 (on BDP). The effect of these different baseline conditions on the relationship of dose frequency to budesonide responsiveness is shown. Each patient subgroup is identified here by the same symbols as in Fig. 1. Subgroup means joined by a line were referenced to the same baseline, either BL1 or BL2. The split in the lines emphasizes that these are intergroup comparisons because data from the first half of the study were referenced to BL1 and data from the second half to BL2. See also Fig. 1 for clarification. Halving the dose frequency had little effect on Δ MLPF as measured by BL2 comparisons but had a readily discernible effect using BL1 comparisons, when the asthma was more unstable.

systemic effects. In a previous comparison of the two drugs in nonasthmatic subjects, budesonide had less systemic effect than BDP on EOS and plasma cortisol levels and greater topical anti-inflammatory potency (on skin).²⁰ In this study there is evidence to suggest an additive systemic effect of budesonide and oral prednisone in the patients who received both drugs (Fig. 3). However, there was such a large intersubject variance in both groups (prednisone users vs non-users) that the differences were far from significant by ANOVA (Δ EOS, $p = 0.69$, Δ SC, $p = 0.49$).

Dose frequency

Giving the same daily dose of budesonide by different dosing frequencies did not affect the drug's apparent systemic potency in these patients as measured by their morning EOS and SC levels, but it did affect its antiasthmatic potency (Fig. 5). Halving the frequency was associated with a major reduction in potency as judged by the drop in daily peak flows

(Δ MLPF, $p = 0.002$). This was coupled with an increase in symptom severity (Δ CISP). Although the latter did not attain statistical significance (Δ CISP, $p = 0.09$), the failure to do so could be due in part to the duration of each treatment period—too short to demonstrate the maximum possible effect of differences in dose frequency. Another factor is the previously mentioned imbalance between baselines, which tended to vitiate the overall influence of dose frequency on all the response indices, including CISP. From the risk-benefit plot shown in Fig. 7, it is apparent that at any given level of "risk" (expressed indirectly in terms of the amount of systemic absorption), greater benefit was consistently achieved by q.i.d. than by b.i.d. dosing.

Several studies have examined the influence of varying the dose frequency on the efficacy of aerosol steroid treatment. Of these, one agrees with the findings in this study,²⁶ whereas others report contradictory results.^{13, 27, 28, 29} The discrepancies could be the result of differences among the response indices used; for example, in this study the influence of dose frequency was highly significant with either 14 day or 7 day averages of daily measurements of peak flow (Δ MLPF, $p < 0.005$ for each) but statistically nonsignificant (though evident) with Δ FEV₁ measured only once at the end of each treatment combination. Another very important factor is the baseline state of the patients' asthma. As illustrated in Fig. 6, an effect of dose frequency on Δ MLPF was clearly evident in our patients when comparisons were made relative to a time when their asthma was active (BL1, on placebo) but was barely discernible when their asthma was better controlled (BL2, on 400 μ g/day BDP). Another consideration is possible differences in patient compliance—between studies and/or between dose frequencies within a study. Poor compliance with the ostensible dosing frequencies could account ipso facto for the absence of any detectable difference between their respective therapeutic outcomes. In this study we measured patient compliance objectively and confirmed that it was high with both the dosing frequencies compared.

The important effect of dosing frequency on budesonide efficacy as shown by these data has not been studied with other topically active steroids. Since budesonide has a higher topical anti-inflammatory potency than BDP or triamcinolone acetonide and, unlike BDP, it does not undergo partial biotransformation in the lung,²¹ it seems likely that the antiasthmatic efficacy of these other drugs would be even more frequency dependent than budesonide, although their respective absorption rates from the lung must also be considered. Flunisolide is known to be effec-

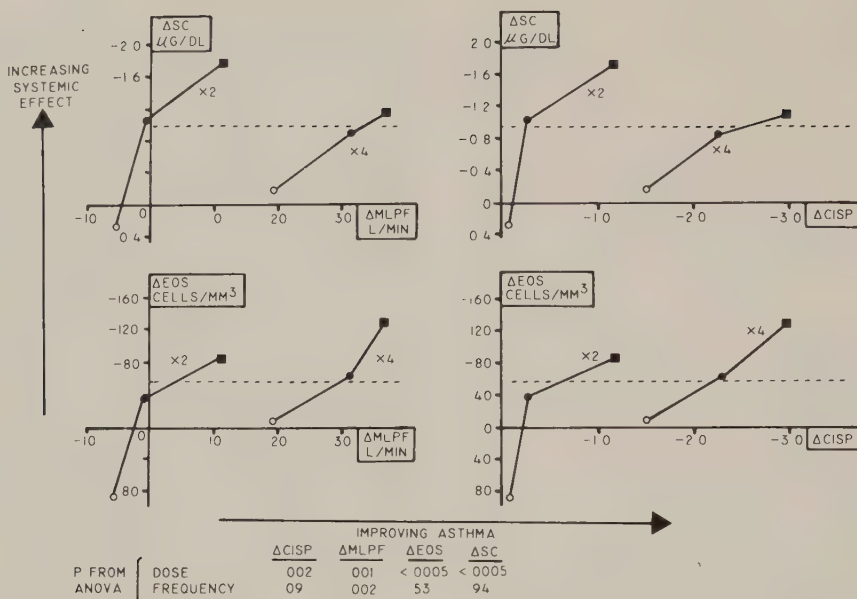


FIG. 7. Systemic effects of budesonide are plotted on the vertical axes (upper, ΔSC ; lower, ΔEOS), and the local (antiasthmatic) effects are plotted on the horizontal axes (left, $\Delta MLPF$; right, $\Delta CISP$). The points are pairs of means at each of the budesonide dose levels: 400 μg ($\circ$), 800 μg ($\bullet$), ad 1600 $\mu g/day$ ($\blacksquare$). For any given level of systemic steroid effect (arbitrarily indicated, for example, by the dashed lines), q.i.d. dosing achieved greater airflow improvement ($\Delta MLPF$, $p < 0.005$) and symptom reduction ($\Delta CISP$, $p = 0.09$) than b.i.d. dosing.

tive if given b.i.d.³⁰ (as is budesonide, Fig. 5), but there are no published data that define the particular importance of different dose frequencies on the antiasthmatic potency of flunisolide. Until further data become available it would seem clinically prudent to assume that the response-limiting influence of dosing frequency demonstrated in this study is a general characteristic of the various inhaled steroids used to treat asthma.

Dose scheduling

The significant interaction of dose scheduling on ΔSC illustrated in Fig. 4 could be interpreted either as a reflection of suppression of HPA function by A.M. administration of low doses of budesonide or conservation by A.M. administration of high doses. The latter seems more likely, given the findings of previous investigators about the negligible systemic activity of budesonide at 400 $\mu g/day$.²⁰ Thus we interpret these results as indicating that morning dosing spares HPA function if the daily dose of budesonide is increased above 1000 μg , but it has no similar sparing effect on the direct actions of the systemically absorbed drug, as represented by ΔEOS (Fig. 4). Presumably the different effects of the dosing schedule on ΔSC and on

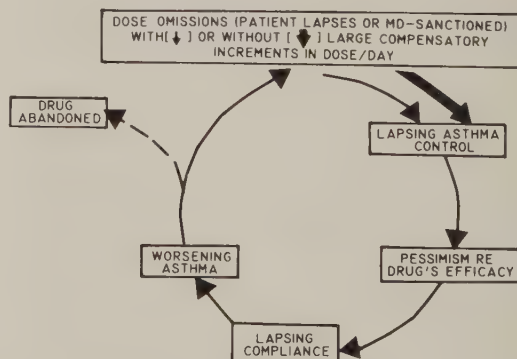


FIG. 8. Schema illustrating how reductions in dosing frequency could lead to slow and progressive deterioration in the patient's asthma and eventually to abandonment of the drug, while the cause-and-effect relationship between the dose reduction and the clinical course remains unrecognized.

ΔEOS reflects their different physiologic control mechanisms—SC being normally subject to a circadian feedback control system via the HPA axis, to which EOS is not subject. It is possible that ΔEOS may be a better predictive index than ΔSC for the complications that result from the more direct actions

of glucocorticoids on various nonpulmonary tissues independent of HPA axis-mediated mechanisms, e.g., osteoporosis, growth stunting, or cataract formation.³¹⁻³³

The reduction in efficacy associated with the shift to A.M. dosing was much less than that which resulted from halving the dose frequency (see Figs. 4 and 5). However, because of the vitiating effect on the treatment responses of the previously mentioned short observation periods and the different baseline treatments (see Fig. 6 and Methods), relative potencies derived from this study must be viewed as minimum estimates, smaller than those expected if it had been feasible to give placebo in both baseline periods. We interpret the data as indicating a marginal reduction in efficacy with morning dosing, which might well increase after longer treatment to the point of becoming troublesome in any patient with unstable asthma.

The applicability of these findings to aerosolized steroids other than budesonide is unknown. Only one relevant study has been reported.³⁴ High-dose BDP was used, and essentially the same results were seen; that is, a shift to morning dosing was associated with a rise in morning cortisol levels, without any appreciable reduction in efficacy. However, interpretation of that study is uncertain because it did not control for the possible influence of seasonal differences in asthmagenic challenge. In the study reported here, possible error of that sort was controlled by balancing the order of the treatment combinations across the 30 wk protocol, as shown in Fig. 1.

Implications for clinical practice

At every dose level of budesonide, and regardless of the response index measured, the best results in these patients were consistently seen with q.i.d. A.M./P.M. dosing. Although the data confirm that switching to morning dosing can conserve endogenous HPA function when high doses are used (Δ SC, Fig. 4) this study has not proved that such a regimen is of real clinical value in reducing risk, since it may not confer an equivalent reduction in the risk of those adverse effects that result from the more direct actions of high-dose steroid on peripheral cells (Δ EOS, Fig. 4). Susceptibility to such risks varies considerably among patients, some being resistant to glucocorticoid side effects despite high dosage because of inherent or acquired differences in their steroid pharmacokinetics,^{35,36} or other patient characteristics that are not yet well defined.³⁷ Therefore, in practice, decisions about aerosol steroid dosage should be based on individualized risk-benefit judgments. However, two generalizations can help to reduce the overall risks of

treatment. (1) The daily dose should be kept as low as is consistent with good control of the asthma, by taking advantage of the ability of oral bronchodilators to augment the clinical response in asthmatic patients receiving aerosol steroids.³⁸ (2) Dosing frequency should be kept high, since as shown in this study, increasing the dose frequency of an aerosol steroid can increase its efficacy without any increase in the daily dose (or systemic absorption).

Aside from its value for reducing risk, frequent dosing may also play a useful role in helping to maintain patient compliance during aerosol steroid therapy. Reductions in dose frequency, made purposely in the hope of improving patient compliance and thus conserving long-term efficacy, could have paradoxical results. The relationships illustrated in Fig. 6 indicate that while less frequent dosing may be tolerable without appreciable loss of efficacy during periods of asthma remission, dose frequency becomes a response-limiting factor when the disease relapses, as chronic asthma characteristically does sooner or later. Several reviews of BDP therapy^{8, 11, 39} mention a decline in efficacy of the drug as it is used for longer periods, an observation supported by the occurrence of late treatment failures after an initial period of success. None of these reviews has taken dosing frequency into account as a possible factor to explain such failures. The schema in Fig. 8 outlines how reductions in dose frequency might lead to the abandonment of aerosol steroid treatment for reasons related essentially to the dosing regimen rather than to the drug per se. Concomitant reduction in the dose/day (the usual corollary of an unscheduled omission of a dose) would of course further aggravate the problem because daily dose is another major determinant of efficacy (Fig. 2).

To ensure that patients continue to comply with the desired dosing frequency it is necessary to repeatedly reinforce the dosing instructions. Cost-effectiveness provides a persuasive logic to support such advice. From an examination of the effects of daily dose and frequency on Δ MLPF as shown in Fig. 5, it is evident that it is more cost-effective for a patient to double the frequency of dosing than to quadruple the dose of the drug. He or she can increase the amount of asthma control without increasing drug costs by simply increasing the number of doses per day. If that is not convincing, risk-benefit considerations may be. As Fig. 7 shows, increasing the dose frequency can increase antiasthmatic efficacy without significantly increasing the systemic effects of the drug, whereas increasing the number of puffs per dose does not accomplish the same thing.

We gratefully acknowledge the cooperation of the patient volunteers who participated in this study, and special assistance from Mrs. Asta Eskildsen and staff of the Pulmonary Function Laboratory, Adele Persaud, R.T., J. Anderson, R.T., and Ray Fynes, M.B., B. Ch., Vice President, Scientific Affairs, Astra Pharmaceuticals, Canada Ltd. Data processing was done by the Victoria Hospital Medical Research Biostatistics Unit directed by George Wells, Ph.D.

REFERENCES

1. Morrow-Brown H, Storey G, George WHS: Beclomethasone dipropionate: a new steroid aerosol for the treatment of allergic asthma. *Br Med J* 1:585, 1972.
2. Costello JF, Clark TJH: Response of patients receiving high dose beclomethasone dipropionate. *Thorax* 29:571, 1974.
3. McAllen MK, Kochanowski SJ, Shaw KM: Steroid aerosols in asthma: an assessment of betamethasone valerate and a 12-month study of patients on maintenance treatment. *Br Med J* 1:171, 1974.
4. Williams MH, Kane C, Shim CS: Treatment of asthma with triamcinolone acetonide delivered by aerosol. *Am Rev Respir Dis* 109:538, 1974.
5. British Thoracic and Tuberculosis Association: A controlled trial of inhaled corticosteroids in patients receiving prednisone tablets for asthma. *Br J Dis Chest* 70:95, 1976.
6. Kriz RJ, Chmelik F, do Pico G, Reed CE: A short-term double-blind trial of aerosol triamcinolone acetonide in steroid-dependent patients with severe asthma. *Chest* 69:455, 1976.
7. Toogood JH, Lefcoe NM, Haines DSM, Jennings B, Errington N, Baksh L, Chuang L: A graded dose assessment of the efficacy of beclomethasone dipropionate aerosol for severe chronic asthma. *J ALLERGY CLIN IMMUNOL* 59:298, 1977.
8. Godfrey S, Balfour-Lynn L, Tooley M: A three to five year follow-up of the use of the aerosol steroid beclomethasone dipropionate in childhood asthma. *J ALLERGY CLIN IMMUNOL* 62:335, 1978.
9. Grieco MH, Dwek J, Larsen K, Rammohan G: Clinical effect of aerosol triamcinolone acetonide in bronchial asthma. *Arch Intern Med* 138:1337, 1978.
10. Bacal E, Patterson R: Long-term effects of beclomethasone dipropionate on prednisone dosage in the corticosteroid-dependent asthmatic. *J ALLERGY CLIN IMMUNOL* 62:72, 1978.
11. Williams MH Jr: Drugs five years later: beclomethasone dipropionate. *Ann Intern Med* 95:464, 1981.
12. Blackwell B: The drug regimen and treatment compliance, in Haynes RB, Taylor DW, Sackett DL, editors: Compliance and health care. Baltimore, 1979, Johns Hopkins University Press, pp. 144-156.
13. McCoy RJ, Laby B: Beclomethasone dipropionate in twice daily treatment of asthma. *Aust Fam Phys* 9:721, 1980.
14. Myles AB, Bacon PA, Daly JR: Single daily dose corticosteroid treatment. *Ann Rheum Dis* 30:149, 1971.
15. Toogood JH, Baskerville JC, Jennings BH, Lefcoe NM: Optimal dosage in steroid-dependent asthma, in Mygind N, Clark TJH, editors: Steroid treatment for asthma and rhinitis. London, 1980, Balliere Tindall, pp. 107-22.
16. Toogood JH, Lefcoe NM, Haines DSM, Chuang L, Jennings B, Errington N, Baksh L, Cauchi M: Minimum dose requirements of steroid-dependent asthmatic patients for aerosol beclomethasone and oral prednisone. *J ALLERGY CLIN IMMUNOL* 61:355, 1978.
17. CIBA Symposium: Terminology, definitions, and classifications of chronic pulmonary emphysema and related conditions. *Thorax* 14:286, 1959.
18. American Thoracic Society: Chronic bronchitis, asthma and pulmonary emphysema. A statement by the Committee on Diagnostic Standards for Nontuberculous Respiratory Diseases. *Am Rev Respir Dis* 85:762, 1962.
19. Thalen A, Brattsand R: Synthesis and anti-inflammatory properties of budesonide, a new non-halogenated glucocorticoid with high local activity. *Arzneimittelforschung* 29:1687, 1979.
20. Johansson SA, Andersson KE, Brattsand R, Gruvstad E, Hedner P: Topical and systemic glucocorticoid potencies of budesonide and beclomethasone dipropionate in man. *Eur J Clin Pharmacol* (in press).
21. Ryrfeldt A, Andersson P, Edsbacker S et al: Pharmacokinetics and metabolism of budesonide, a selective glucocorticoid. *Eur J Respir Dis* 63(Suppl. 122):86, 1982.
22. Toogood JH, Lefcoe NM, Buck C, McCourtie DR: A clinical index of disability due to chronic asthma tested during a trial of cromolyn sodium treatment. *Chest* 63:881, 1973.
23. Murphy BEP: Some studies of the protein-binding of steroids and their application to the routine micro and ultramicro measurement of various steroids in body fluids by competitive protein-binding radioassay. *J Clin Endocrinol Metab* 27:973, 1967.
24. Ellul-Micallef R, Hansson E, Johansson SA: Budesonide: a new corticosteroid in bronchial asthma. *Eur J Respir Dis* 61:167, 1980.
25. Bjorkander J, Formgren H, Johansson SA, Millqvist E: Methodological aspects on clinical trials with inhaled corticosteroids. *Eur J Respir Dis* 63(Suppl. 122):108, 1982.
26. Dahl R, Johansson SA: Inhaled budesonide. Clinical effect of B.I.D. and Q.I.D. administration. A double blind controlled study. *Eur J Respir Dis* 63(Suppl. 122):268, 1982.
27. Munch EP, Taudorf E, Weeke B: Dose frequency in the treatment of asthmatics with inhaled topical steroid. *Eur J Respir Dis* 63(Suppl. 122):143, 1982.
28. Willey RF, Godden DJ, Carmichael J et al: Comparison of twice daily inhalation of a new corticosteroid budesonide with beclomethasone dipropionate four times daily in the treatment of chronic asthma. *Br J Dis Chest* 76:61, 1982.
29. Stiksa G, Glennow C, Johannesson N: An open cross-over trial with budesonide and beclomethasone dipropionate in patients with bronchial asthma. *Eur J Respir Dis* 63(Suppl. 122):266, 1982.
30. Slavin RG, Izu AE, Bernstein IL et al: Multicenter study of flunisolide aerosol in adult patients with steroid-dependent asthma. *J ALLERGY CLIN IMMUNOL* 66:379, 1980.
31. Morris HG, Jorgensen JR, Elrick H, Goldsmith RE: Metabolic effects of human growth hormone in corticosteroid-treated children. *J Clin Invest* 47:436, 1968.
32. Southren AL, Gordon GG, Yeh HS, Dunn MW, Weinstein BI: Receptors for glucocorticoids in the lens epithelium of the calf. *Science* 200:1177, 1978.
33. Loeb JN: Corticosteroids and growth. *N Engl J Med* 295:547, 1976.
34. Toogood J, Jennings B, Lefcoe N: Morning-dose beclomethasone aerosol (BA) treatment is clinically effective and spares adrenal function. *Ann R Coll Phys Surg (Can)* 13:110, 1980.
35. Kozower M, Veatch L, Kaplan MM: Decreased clearance of prednisolone, a factor in the development of corticosteroid side effects. *J Clin Endocrinol Metab* 38:407, 1974.

36. Gambertoglio JG, Vincenti F, Feduska NJ, Birnbaum I, Salvatierra O, Amend WJC: Prednisolone disposition in cushingoid and noncushingoid kidney transplant patients. *J Clin Endocrinol Metab* **51**:561, 1980.
37. Skalka HW, Prchal JT: Effect of corticosteroids on cataract formation. *Arch Ophthalmol* **98**:1773, 1980.
38. Nassif EG, Weinberger M, Thompson R, Huntley W: The value of maintenance theophylline in steroid-dependent asthma. *N Engl J Med* **304**:71, 1981.
39. Gwynn CM, Smith MJ: Long-term results with beclomethasone dipropionate aerosol in children with bronchial asthma: why does it sometimes fail? *Br J Clin Pharmacol* **4**:2695, 1977.
40. Ferris BG: Respiratory disease questionnaire ATS-DLD-78-A in epidemiology standardization project. *Am Rev Respir Dis* **118**:1, 1978.

